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Chronic spontaneous urticaria: cutaneous reaction and laboratory aspects

Urticária crônica espontânea: reatividade cutânea e aspectos laboratoriais

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ABSTRACT

Introduction: The chronic spontaneous urticaria (CSU) is a cutaneous reaction characterized by the formation of episodic and recurrent erythematous papules, usually pruritic, which etiology may be associated with an autoimmune response resulting from the action of immunoglobulin subclass G (IgG) of autoantibodies directed against the immunoglobulin subclass E (IgE) receptors of cutaneous mast cells or against IgE bound to mast cells. The autologous serum skin test (ASST) is a screening test that indicates the presence of these autoantibodies in patients with CSU. **Objective:** To check for differences in ASST results among patients with CSU and the control group with other hypersensitivities. **Material and method:** This is a cross-sectional case-control study, in which 49 adults were analyzed, 27 with CSU and 22 with other hypersensitivity reactions. ASST, CD123, estimation of IgG bound to basophil, mean platelet volume (MPV), antinuclear antibody (ANA), thyroid-stimulating hormone (TSH), anti-thyroid peroxidase antibody (TPOab), erythrocyte sedimentation rate (ESR) and the total IgE were performed in both groups. **Results:** The ASST, shown positive results in 16 (59.2%) the patients with CSU and in five (22.7%) from the control group, with statistical significance. For the other variables above described, there was no statistical difference. **Conclusion:** A higher ASST positivity was found in CSU patients compared to patients with other hypersensitivities, and further studies with larger sample are needed for better analysis of other variables.

Key words: urticaria; skin; intradermal tests; hypersensitivity.

INTRODUCTION

The chronic spontaneous urticaria (CSU) shows a cutaneous reaction characterized by the formation of episodic and recurrent erythematous papules usually pruritic[1, 2]. These lesions result from vasodilation and dermal edema. Since such involvement occurs in the deeper regions of the dermis and subcutaneous and submucosal tissue, the clinical presentation is known as angioedema or angioneurotic edema, manifested mainly by facial swelling (especially the eyelids and lips)[2, 3].

Urticaria and angioedema are common diseases that affect 15% to 25% of individuals at some stage of life[4].

Chronic urticaria (CU) has worldwide prevalence ranging from 0.1% to 0.5%, however we still do not have these estimates for the Brazilian population[4].

The urticaria is classified as acute or chronic according to the duration of symptoms; in acute form, the symptoms persist for up to six weeks, while in the chronic variant, involves the cases which duration exceeds this period of time[3, 4].

CSU or chronic idiopathic urticaria (CIU) refers to the situation in which the apparent cause is not identified. It is believed that approximately 50% of urticarias said "idiopathic" are autoimmune resulting from the action of the immunoglobulin subclass G autoantibodies (IgG) directed against the immunoglobulin subclass E (IgE) receptors of the cutaneous mast cells or against the IgE bound to mast cells[3-7].

Currently, the laboratory diagnosis of chronic autoimmune urticaria (CAU) have as the gold standard the basophil degranulation stimulation test, a laboratory examination (*in vitro*) difficult to perform and costly, used only in major research centers[8, 9].

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Sabroe *et al*. (1999)[9] introduced an *in vivo* test, easy to perform, named autologous serum skin test (ASST) or auto-serum test, for the suspected autoimmune urticaria cases, with sensitivity and specificity reaching about 70%[9], which positive predictive value (PPV) ranges from 48% to 85%, depending on the analyzed study[10].

Some aspects are interesting when studying the pathophysiology of CSU. For example, it is known that the interleukin-3 (IL-3) implies the activation of mast cells and basophils, as well as the CD123 molecule, IL-3 receptor, which are closely related to the initial stage of basophils activation[11, 12]. We also know about the CSU association with positive antinuclear antibody (ANA) and positive anti-thyroid peroxidase antibody (TPOab)[13], and possible changes in mean platelet volume (MPV), which have been recently studied and correlated with urticaria. Another assumption would be the possibility of detecting the presence of autoantibodies directed against the membrane of basophils by searching non-specific IgG antibodies, which could represent IgE anti-receptor antibody or anti-IgE bound to basophil – a simpler and cheaper method which, in a positive result, would enhance the possibility of autoimmune etiology in CSU[10, 11, 14].

The study, therefore, from these aspects – autoantibodies, especially ANA and anti-thyroid antibody CD123 molecule, MPV and ASST – is important for understanding the pathophysiology of CSU.

OBJECTIVE

To check for differences in the ASST results the group of patients with CSU and the control group consisting of patients with other types of hypersensitivities, as well as on the following laboratory tests: CD123, IgG bound to basophils, MPV, TPOab, ANA, erythrocyte sedimentation rate (ESR), total IgE.

MATERIAL AND METHOD

This is a cross-sectional case-control performed in the outpatient allergy and immunopathology clinics of the Faculdade de Medicina de Marília, where ASST was performed. Other tests were performed in the Blood Center of the above-mentioned College.

The ASST technique consists of collecting blood in dry tube without additives. We wait about 30 minutes at room temperature to clot retraction and centrifuged 400 g to 500 g per 10 minutes. Then, asepsis and demarcation of skin procedures have been performed. We administered intradermal 0.05 ml of patient serum and saline solution as negative control; also, for positive control, a light puncture releasing a drop of histamine was performed, all applications 3 cm distant from each other. We wait 20 to 30 minutes and then, we read with the ruler; results were based on the mean values of the two largest diameter of each papule formed, and the positive result is characterized by erythematous papules round formation with a difference equal to or greater than 1.5 mm between the serum and the negative control averages[10].

For other laboratory tests (ESR, MPV and total IgE), we use the usual techniques; ANA and TPOab by immunoassay, and intensity of CD123 and IgG bound to basophils expressions by flow cytometry.

To calculate the sample size, considering the ASST prevalence in CU patients is about 40% (0.4)[10] and in the control group (patients without urticaria) is 0.025[9], we apply the following formula[15]:

$$n = [Z\alpha\sqrt{2PoQo} + W\beta\sqrt{PaQa + PbQb}]^2/(Pa - Pb)^2$$

Where:

Pa = 0.4 (ASST positive ratio in CU patients)

Pb = 0.025 (ASST positive ratio in patients of the control group)

Qa = 1 – Pa = 0.6

Qb = 1 – Pb = 0.975

Po = Pa + Pb/2 = 0.212

Qo = Qa + Qb/2 = 0.787

$Z\alpha$ for $\alpha = 0.05$. Then $Z\alpha = 1.96$, assuming that the research has statistical significance for p 0.05.

$W\beta$ to a power = 0.9 and $\beta = 0.10$, then $W\beta = 1.28$, so that the research has a power equal to 0.9 to find the true value.

In the analysis of categorical variables we used the odds ratio (OR) calculation with a confidence interval (CI) of 95%. In the statistical analysis of the quantitative variables, the Student t test was used, considering statistical difference for $p < 0.05$.

RESULTS

We evaluated 27 patients with CSU and 22 in the control group (patients with other hypersensitivities). In both groups, there were more females (19 in each group). The mean age and standard deviation (SD) of patients with CSU was 44.6 (± 13.6) years and among those of the control group, 39.8 (± 11) years (**Table 1**).

TABLE 1 – Characteristics of patients evaluated

Analyzed variables	CSU	Control group
Number of individuals analyzed	27	22
Sex	8 M/19 F	3 M/19 F
Average age in years (SD)	44.6 (± 13.6)	39.8 (± 11)

CSU: chronic spontaneous urticaria; M: male; F: female; SD: standard deviation.

The hypersensitivity situations found in the control group patients were: pruritus in one case, rhinitis in 10 cases, hypersensitivity to non-steroidal anti-inflammatory drugs in eight cases, hypersensitivity to the angiotensin-converting-enzyme inhibitor in one case, hypersensitivity to artificial dyes in one case, contact dermatitis in one case, intolerance to chemicals products inhaled in three cases.

Regarding ASST, this was positive in 16 (59.2%) patients with CSU and five (22.7%) of the control group.

In the statistical analysis of the TPOab positive, ANA positive, and the changes in ESR, as well as for the ASST, the OR (95% CI) was used. There was statistically significant only for the ASST. In **Table 2**, these results are shown with their related statistical calculations.

The dotted nuclear represents the ANA standard found in positive patients.

The mean and SD of the intensity of CD123 expression was 1417.7 (± 376) in patients with CSU and 1475.4 (± 463.3) in the control group.

The mean and SD of the intensity of expression of IgE bound to basophils was 55.7 (± 80.3 in patients with CSU and 54.4 (± 49.8) in the control group.

MPV with SD in patients with CSU was 10.6 µl (± 1) and 10.1 µl (± 0.9) in the control group.

The average value and SD of the amount of IgE in patients with CSU was 170.7 (± 201.8) UI/ml and 154.7 (± 194.6) in the control group.

There was no statistical significance for any of the above variables (**Table 3**).

TABLE 2 – Comparison of the prevalence of positive autologous serum test, positive TPOab, positive ANA and high ESR among individuals with CSU and the control group with the respective OR (95% CI)

Analyzed variables	CSU	Control group
Positive autologous serum test	16 (59.2%) OR (95% CI): 4.95 (1.41-17.41)	5 (22.7%)
Positive TPOab	5 (20%) OR (95% CI): 1.13 (0.26-4.85)	4 (18.2%)
Positive ANA	4 (14.8%) OR (95% CI): 0.59 (0.14-2.54)	5 (22.7%)
Alteration in ESR	9 (33.3%) OR (95% CI): 1.17 (0.34-4.06)	6 (30%)

TPOab: anti-tyroid peroxidade antibody; ANA: antinuclear antibody; ESR: erythrocyte sedimentation rate; CSU: chronic spontaneous urticaria; OR: odds ratio; CI: confidence interval.

TABLE 3 – Medium and SD of CD123 expression intensity of IgG bound to basophils, MPV and total IgE in the groups studied

Tests	CSU	Control group	Statistical significance ($p \leq 0.05$)
CD123 (int. of expression [SD])	1417.7 (± 376)	1475.4 (± 463.3)	NSS
IgG bound to basophilic (int. of expression [SD])	55.7 (± 80.3)	54.4 (± 49.8)	NSS
MPV in µl (SD)	10.6 (± 1)	10.1 (± 0.9)	NSS
Total IgE in UI/ml (SD)	170.7 (± 201.8)	154.7 (± 194.6)	NSS

SD: standard deviation; IgG: immunoglobulin subclass G; MPV: mean platelet volume; IgE: immunoglobulin subclass E; NSS: not statistically significant.

DISCUSSION

ASST was initially designed in 1986 by Grattan *et al*. (1993)[5], using serum from patients with CSU. Later, the same authors reported the presence of anti-IgE autoantibodies inducing histamine release in the serum of patients with CSU, demonstrating that individuals with the disease had autoantibodies directed against the high-affinity IgE receptor (FCεRI).

In our research, for the variables of the positive ASST, TPOab, ANA and the changes in ESR, we used OR (95%CI) as a measure of association. Regarding the ASST, we observed that OR (95% CI) was 4.95 (1.41-17.41), which could be stated as follows: there would be 4.95, that is, about five people with positive ASST in the group of patients with CSU for one person with a positive ASST in the control group. In this case, as the CI did not include the value 1, i.e., the range between the CI limits was above 1, we can assert that the result was statistically significant.

In our research, the ASST results showed higher positivity in the group of patients with CSU compared to patients in the control group, with statistical significance. These data are consistent with some studies in the literature in which patients with CSU have more cutaneous reaction compared with patients with other hypersensitivities, such as chronic rhinitis and asthma. Guttman *et al*. (2007)[4] showed positive ASST in patients with CSU compared with patients with respiratory allergies and healthy subjects, totaling 116 patients. In the group of patients with CSU, 53% were positive ASST and, in the group of patients with respiratory

allergies, 29.8% were positive. The healthy controls showed 40.5% positivity[4].

In another study published in 2004 in Italy[16], researchers studied patients with CSU and respiratory diseases such as asthma and allergic rhinitis. ASST was applied to individuals with CSU and also in a group of patients with respiratory disease and a control group with healthy individuals. The positive ASST, in CSU group was 58%, while in patients with respiratory allergy, it was slightly lower (47%)[16].

Celen *et al*. (2014)[17], in the Turkey conducted a study on the usefulness of ASST in patients with CSU. The study recruited 60 patients, 30 of CSU group, and individuals with no systemic or cutaneous diseases, by performing ASST in both groups. The results showed statistically significant difference between the CSU and the control groups, with positivity of 53% and 26.6% respectively[17]. This result was very similar to our study, which found percentages similar to the values with statistical significance.

There are few national studies on the positive ASST. A recent national study, conducted by researchers of the division of allergy and clinical immunology of the Faculdade de Medicina de Marília, studied the epidemiological characteristics of CSU focused on histocompatibility profile and presence of autoantibodies. The total sample was 67 individuals, and ASST was applied to all patients in the study. One of the results was positive ASST in 49 patients (73%), showing a high prevalence of positive ASST in patients with CSU[13].

A second study by the same Brazilian authors examined the expression of the basophil CD63 and CD123 expression markers and the accuracy of ASST in patients with CSU[14]. The study included 33 patients, from the total, 66.6% had positive ASST and 33.3% were negative[14].

Another Brazilian author conducted in 2009 a study on the basophil activation profile, evaluating patients with CSU that underwent ASST. The study included 37 subjects with and a control group with 38 healthy individuals. ASST showed positive results in 17 patients (47.4%)[18]. Analyzing other laboratory tests, the author found positive ASST in 31.25% of those with positive ANA and among patients with positive TPOab, 11.8% had positive ASST[18].

In a recent Brazilian study on ASST in CU, they evaluated 175 individuals by the records of patients with clinical diagnosis of CU. In 72 subjects with idiopathic urticaria, 50 were positive ASST (62.4%)[19]. Among the physical urticarias of 103 patients, as dermographism, heat urticaria, cold urticaria and cholinergic urticaria, 61 were positive ASST (59.3%)[19]. The authors found high rates of positive ASST in patients with idiopathic CU and also in physical urticaria suggesting autoimmune etiology. They emphasize, however, that further studies are needed to establish a real prevalence of positive ASST among patients with CU[19].

ASST has been used as a quick indicator to detect cutaneous autoreactivity *in vivo* tests, but does not define with absolute certainty CSU as an autoimmune disease[1]. According to a review and consensus on ASST, European authors observed that the variation of positive ASST in patients with CSU ranged between 4.1% and 70.6%, and this variation could be related to the selection of patients, severity of the CSU, methodology and interpretation of response in the population tested. According to a review study, some research has shown high prevalence of positive ASST (around 30% to 50%) in adults without CSU but with other allergic diseases, and also a positive ASST around 40% a 45% among healthy individuals. According to the authors, it is relevant to investigate whether the cutaneous reactivity and positive ASST in healthy individuals would be risk factors for CSU development[10].

For the other variables analyzed by the OR, the positive TPOab, ANA and changes in ESR do not show values with statistical significance.

The European guideline, which defines and classifies the diagnosis of CSU, recommended as screening tests the blood count and ESR to help in the diagnosis of the disease[20], which can be changed when there is an inflammatory process or inflammatory underlying disease.

Regarding urticaria specifically, there are few studies addressing the ESR. According to Grattan *et al*. (2002)[21], ESR may be altered in urticarial vasculitis. Another study of 94 children with CSU, aged between 4 and 15 years, observed that 13% had changes in ESR[22].

Another study by Tarbox *et al*. (2011)[23] researched the usefulness of routine laboratory tests in the investigation of CU and angioedema. The research included 200 patients, and of those, 99 individuals were diagnosed with CU/angioedema and only two with angioedema. Elevated ESR was found in 16 patients from 108 of those who performed the test (14.8%)[23].

Miller *et al*. (1968)[24] published a survey on CU in which the ESR was performed in 42 patients, of which 12 with altered result[24].

Regarding autoimmunity, our study compared the presence of ANA autoantibodies and TPOab in CSU and control groups, finding no statistical difference between them, but it is believed that this may have occurred due to the low sample size, because *n* calculation was performed prioritizing the prevalence of ASST. Patients were not differentiated in relation to disease severity.

Viswanathan *et al*. (2012)[25] investigated the role of autoantibodies in the CSU, identifying these biomarkers in the most severe cases. The study included 195 patients with CSU, which were investigated for the presence of ANA antibodies, TPOab and anti-thyroglobulin. The positive ANA was 29%, TPOab was 6%, and anti-thyroglobulin was 26%, and 38% was not positive for any of the antibodies previously mentioned. They concluded that CSU, when associated with the presence of autoantibodies such as ANA, TPOab or anti-thyroglobulin, were directly correlated with the severity of disease[25].

Krupa Shankar *et al*. (2012)[26] published a study regarding the etiology of the CSU. The sample of the survey was 150 individuals who had the disease. They found five (7.7%) with positive ANA[26], somewhat similar in absolute numbers to the result of our study, in which four patients with CSU were positive ANA.

Hipólito (2008)[27] found 20 patients with positive ANA in a total of 48 individuals with CSU (42%); positive TPOab occurred in two patients (14%) and only one was positive for anti-thyroglobulin.

There are few studies published studies in Brazil on ANA and TPOab autoantibodies related to the CSU. In the study conducted by Lourenço *et al*. (2008)[18], ANA was positive in seven of 35 patients with CSU (41.75%), corresponding to 1.25% in the positive ASST group, and 10.5% in the negative ASST group. TPOab was positive in two of 17 patients of positive ASST group (11.8%) and two of 18 patients of the negative ASST group (11.1%).

Another national study has researched the epidemiological characteristics of CSU focused on histocompatibility profile and the presence of the autoantibodies ANA and TPOab. From a total of 49 patients, 15 with positive ANA (22.4%) and seven with positive TPOab (10.5%) were found[13].

In our study, the mean and SD of CD123 expression intensity was 1417.7 (± 376) in patients with CSU, and 1475.4 (± 463.3) in the control group, with no difference between groups.

There are few studies in the literature involving the CSU and CD123, the majority of published works on the CD123 is related to other diseases, such as leukemias and lymphomas.

According to another Brazilian study, it is known that IL-3 expression marker, whose receptor is CD123, is associated with the initial stage of basophil activation and histamine release, and is one of those mechanisms responsible for the emergence of CSU[14]. In this study, Calamita *et al*. (2012)[14] studied the intensity of CD63, CD123 expression markers, the IgG bound to basophils autoantibodies and the accuracy of ASST in CU patients. The study evaluated 33 adult subjects with CU, finding no statistical difference in the intensity of CD123 expression between patients with positive and negative ASST. In the group of patients with positive ASST, the average intensity of CD123 expression was 1209.75 and for the group with negative ASST it was 1432.96.

In another study held by Brazilian authors, Lourenço *et al*. (2008)[17] observed that patients with positive ASST showed increased expression of markers present in the membrane of basophils, such as CD123, with statistical difference. The result found by the authors indicate that CD123 expression was more intense in patients with positive ASST compared with patients with negative ASST.

In our study, the mean and SD of the intensity of IgE bound to basophil expression was 55.7 (± 80.3) in patients with CSU, and 54.4% (± 49.8) in the control group, with no statistical difference. We performed the non-specific IgG measuring, test on which there are few research related to CSU published. There are some works on high-affinity specific IgG receptor (FcεRI) of basophil, but it is not the same test which we performed in our study.

Swerdt *et al*. (2005)[11] published an article on the detection of IgG autoantibodies in CSU and induction of CD63 expression marker. The authors used the serum of 61 patients with CSU and the serum of 23 patients that constituted a control group, with a history of asthma, eczema and hay fever season. The positive basophil activation induced by IgG was 51% in patients with CSU, and in the control group, 6.59% with statistical difference.

Kaplan e Kikuchi (2001)[28] studied the autoimmune mechanisms of basophils activation in CU. The authors concluded that a population of patients with CU have IgG antibodies directed to the FCεRI. These circulating IgG antibodies activate basophils and, subsequently, the release of histamine; this is one of the pathophysiological mechanisms of CU.

The Brazilian study by Calamita *et al*. (2012)[14] held a measurement of non-specific as in our study. According to the authors, the detection of non-specific IgG autoantibodies could have a correlation with the presence of specific IgG antibodies against the FCεRI or against the IgE bound to basophils itself. In this study, which involved 33 adults with CSU, comparing a group of patients with positive ASST and negative ASST, no statistical difference between the non-specific IgG bound to basophils expression was found in both groups.

We believe that, regarding the non-specific IgG, although our results do not show any trend that could indicate a potential increase of it in patients with CSU, it would be interesting to increase the sampling to clarify more accurately such matter.

In our study, the MPV and SD in patients with CSU was 10.6 µl (± 1), and 10.1 µl (± 0.9) in those patients in the control group, results with no statistical significance.

Regarding the MPV related to the CSU, also, few works involving this examination and its relationship with CU were published.

Some studies on the MPV in CU reported that it may be increased or decreased; therefore, the data are controversial. These data are conflicting due to the difficulty in excluding other factors that may cause this increase or the decrease.

Magen *et al*. (2015)[29] found MPV increased in patients with CSU and positive ASST.

Confino-Cohen *et al*. (2012)[30] used data from 12,778 CU patients and a control group with 10,714 patients without urticaria, who had visited dermatologists and allergists for 17 years in a health center in Israel. MPV was increased in 28.5% in patients with CU ($n = 3.662$), compared with 1.2% in the patients of control group ($n = 129$) with statistical difference.

In our research, we found a trend for MPV higher in patients with CSU in relation to the control group, but with no statistical significance. To know whether this trend could be confirmed or not, it would be required increasing sample size.

We also note that the mean and the SD values of the IgE amount in patients was 170.7 ul/ml (± 201.8) and in the control group was 154.7 ul/ml (± 194.6), no statistical difference between the results was found.

Kessel *et al*. (2010)[31] studied 203 patients with CSU and a control group of 81 healthy individuals. The total IgE was increased in 69 patients in the CSU group (34%), and seven patients in the control group had increased total IgE (8.5%) levels, with statistical difference. In this study, it was concluded that the total IgE levels are often increased in patients with CU, and is associated with the severity and duration of disease[31]. We need also to emphasize that in the study of Kessel *et al*. (2010)[31], the control group consisted of healthy patients, different from ours, which was formed by patients with other allergies. An important point to be stressed is that in our study, the control group consisted of patients with other allergic conditions in which it is usually also expected an increase in the IgE levels, therefore, the fact we did not find statistical difference between IgE levels in the studied groups is understandable.

CONCLUSION

We found statistically significant differences only for the ASST in the CSU group compared to our control group consisted of patients with other types of hypersensitivity. In other laboratory tests, we found no statistical difference, which may be related to the low sample size of this research. However, it is considered interesting to investigate these variables in future studies.

There are few Brazilian studies on this subject, thus, this research will contribute to the expansion of knowledge and confirm relevant information and data about the CSU, besides addressing recent studies on CSU, ASST and other laboratory tests involved in this study.

RESUMO

Introdução: *A urticária crônica espontânea (UCE) é uma reação cutânea caracterizada pela formação de pápulas eritematosas episódicas e recorrentes, em geral, pruriginosas, cuja etiologia pode estar relacionada com uma reação autoimune decorrente da ação de autoanticorpos de imunoglobulinas da classe G (IgG), dirigidos contra receptores da imunoglobulina da classe E (IgE) dos mastócitos cutâneos, ou contra IgE ligadas aos mastócitos. O teste do soro autólogo (TSA) é um exame de triagem que sugere a presença desses autoanticorpos em pacientes com UCE.* ***Objetivo:*** *Verificar se existem diferenças nos resultados do TSA entre os pacientes com UCE e os de um grupo-controle com outras hipersensibilidades.* ***Material e método:*** *Trata-se de um estudo transversal de caso-controle, no qual foram analisados 49 adultos, sendo 27 com UCE e 22 com outras reações de hipersensibilidades. Foram realizados TSA, CD123, pesquisa de IgG ligada ao basófilo, volume plaquetário médio (VPM), fator antinuclear (FAN), hormônio estimulador da tireoide (TSH), antitireoperoxidase (anti-TPO), velocidade de hemossedimentação (VHS) e IgE total em ambos os grupos.* ***Resultados:*** *O TSA demonstrou resultados positivos em 16 (59,2%) pacientes com UCE e em cinco (22,7%) do grupo-controle, com significância estatística. Para as demais variáveis descritas acima, não se encontrou diferença estatística.* ***Conclusão:*** *Constatou-se maior positividade do TSA nos pacientes com UCE em relação aos pacientes com outras hipersensibilidades, sendo que, para melhor análise das demais variáveis, são necessários outros estudos envolvendo maior amostragem.*

Unitermos: *urticária; pele; testes intradérmicos; hipersensibilidade.*

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