

Provocation test on stairs: a new accessible method to cholinergic urticaria diagnosis

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Summary

Background. Cholinergic urticaria (CholU) is characterized by itching and/or stinging, painful micro wheals due to systemic heating. There are two standardized protocols to diagnose CholU using an exercise bike with heart rate or warming passive. The objective is to provide an affordable, new, low-tech test to assist the diagnostic. **Methods.** Cross-sectional study with a convenience sample; 10 with a diagnostic or high suspicion of CholU and 20 participants without suspicion of CholU, recruited in a UCARE from a developing country. After the pre-participation assessment, the provocation test through movements of going up and down a flight of stairs and with a heart rate monitor, an increasing 15 bpm every 5 min until an increase of 90 bpm above the initial level, for 30 min and/or stopped immediately, upon visualization of wheals and with body temperature measured in 3 different locations every 5 min. **Results.** The group CholU comprised eight females and two males (29.6y), and the other group had eleven females and nine males (27.2y). Data analysis demonstrated that in a positive test in a body temperature measured above 37.05°C and with a variation of 0.35°C above the initial value, sensitivity of 80% and specificity of 100% in the forehead region and sensitivity of 80% and specificity of 90% in tympanic region. **Conclusions.** Thus, with the feasibility of reproducing the method, it is expected that this simple and accessible method for diagnosing CholU can be a tool for application, mainly in developing countries.

Key words

Cholinergic urticaria; chronic inducible urticaria; provocation test.

IMPACT STATEMENT

This study aims to publicize the presentation of a new diagnostic technique with low technological and safe input, seeking to assist diagnosis outside reference centers and in developing countries.

ABBREVIATIONS

CholU – Cholinergic urticaria; UCARE: Urticaria Centers of Reference and Excellence; CIndU: Chronic Inducible Urticaria; HDI: Human Development Index; B.M.I.: Body Mass Index; PAR-Q: Physical Activity Readiness Questionnaire

Introduction

Urticaria is characterized by the appearance of wheals, angioedema, or both. Chronic urticaria (≥ 6 weeks) can occur spontaneously (Chronic Spontaneous Urticaria) or be motivated by specific stimulation (Chronic Inducible Urticaria), which is reported through provocation tests (1).

Cholinergic urticaria (CholU) is a subtype of chronic inducible urticaria with sweat in its genesis and occurs due to systemic heating (2,3). CholU is characterized by itching and/or stinging, painful papular wheals (1-3 mm) that develop simultaneously with sweating, related to increased body temperature from physical exercise, hot baths, stress, spicy foods or hot drinks; symptoms generally disappear within 1 hour, and these sensations are highly impacted to disturb the quality of life (4). CholU has its incidence and prevalence predominantly between the second and third decades of life (5,6).

There is consensus that an increase in body temperature above 1 °C from baseline, as indicated by a passive warming test while sitting for ≤ 15 min in a 42°C water bath, confirms the diagnosis of CholU (10). A standardized protocol was proposed to diagnose CholU using an exercise bike with heart rate and temperature control. The patient positions himself on the

exercise bike and begins pedalling, being instructed so that the pulse increases by 15 bpm every 5 min, reaching 90 bpm above the basal level after 30 min (14). The time for urticaria to appear is inversely proportional to the intensity of the disease; therefore, the shorter the time for the lesions to occur, the more severe cholinergic urticaria is considered (7-14).

In this way, the site team of this study asked if it would be possible to provide a simple, affordable, low-tech test with statistically reliable indices to assist specialists and primary care diagnoses, especially in environments outside reference centers and in developing countries.

Methods

Cross-sectional intervention study with a convenience sample, in which 30 participants were divided into two groups: 10 with a diagnostic and/or high clinical suspicion of CholU and twenty participants without clinical suspicion of CholU and with other CIndU, who were recruited from the UCARE Immunology Service outpatient clinic in a developing (HDI = 0,76) and tropical country. All were between 12-65 years old, both sexes and B.M.I. (18.5-30 kg/m²).

The exclusion criteria were to avoid corticosteroids for 15 days, antihistamines for 7 days, or anti-IgE therapies for 6 months before the test. They should not regularly use immunosuppressive therapy, have a comorbidity that makes it impossible to practice physical activity, have been suspected of exercise-induced anaphylaxis, or have skin comorbidities that could make it impossible to assess the body surface. The patient should not have performed physical exercise in the last 24 hours before the test or ingested stimulant medications.

On the previous visit, the participant underwent a complete clinical examination, electrocardiogram, and Physical Activity Readiness Questionnaire (PAR-Q) to avoid unfavourable outcomes and increase safety in the test. On the second day (7 to 15 days after the first visit), the participants underwent the CholU Provocation Test on stairs. The acclimatization time was 20 min, during which the participant underwent temperature measurement in 03 sites (forehead, oral and tympanic) using a digital infrared thermometer. The

Provocation Test was carried out in a room or auditorium with a controlled ambient temperature of 20–23 °C by moving up and down a flight of stairs (13 steps) with a slow. It gradually increased initial speed through the evaluator's commands, aiming to obtain an increase of 15 bpm every 5 min until a rise of 90 bpm above the initial level, for 30 min. A heart rate monitor (Polar F11®) was adapted to the patient's chest using a chest strap suitable for the instrument and to the wrist using a watch-type marker. (Figure 1)

The provocation test was stopped immediately, regardless of the period elapsed, upon visualization of pruritic wheals associated with erythema characteristic of CholU. Body temperature was measured in 3 different locations every 5 min with interruptions that did not exceed 10 seconds. In addition, a small amount of starch and iodine was placed on the individual's dorsal region to analyze the positivity regarding the appearance of sweat during the diagnostic test. The ambient temperature (°C) and relative humidity (%) were measured.

The research (CAAE 57071122.6.0000.5257) was approved by the local ethics committee on August 4, 2022, after being submitted for consideration by CEP/HUCFF-UFRJ (C.E.P. number: 5.562.556.).

Results

The sample from the group CholU was composed of eight female and two male participants, with an average age of 29.6 years (18-55y) and an average body mass index of 23.5 kg/m² (20.2–28.8 kg/m²). Proportionally, the control group had eleven female and nine male participants, with an average age of 27.25 years (19-52y) and an average body mass index of 24.2 kg/m² (21.4–29.2y).

All patients presented a reactive starch-iodine test during physical activity, demonstrating sweat associated with the test. Among the control group, 14 individuals were observed with dermatographism, four with cold urticaria, one with vibratory urticaria and another with solar

urticaria. All tests were conducted at a controlled temperature between 20°C and 23°C, with an average relative humidity of 66% (58%-72%).

The final temperatures among the subjects and sites were: Final oral temperature of the group with CholU (average 37.1°C, standard deviation 0.277) vs participants without CholU (average 36.85 °C, standard deviation 0.161) p-value=0.013. The forehead temperature in the study group with CholU (average 37.17 °C, standard deviation 0.295) vs control group (average 36.88 °C, standard deviation 0.159), p-value=0.001. The tympanic temperature in the study group with CholU (average 37.14 °C, standard deviation 0.26) vs control group (average 36.9 °C, standard deviation 0.13), p-value=0.002. All patients with positive provocation tests presented an increase of 0,5°C compared to basal temperature. (Figure 2)

Data analysis demonstrated that in a positive CholU provocation test, presenting clinical characteristics compatible with the disease, in a temperature measured in the forehead region above 37.05°C and with a variation of 0.35°C above the initial temperature value, sensitivity is 80% and specificity is 100%.

A positive provocation test for CholU, presenting compatible clinical characteristics, at a temperature measured close to the tympanic region above 37.05°C and with a variation of 0.35°C above the initial temperature value, sensitivity is 80% and specificity of 90 %. The oral temperature did not present statistically relevant values. However, it showed an increase in temperature like the other sites and above the control group. (Figure 3 and 4)

Discussion and Conclusion

This study looked for a simple, affordable, low-tech test that could help diagnose CholU, especially in environments outside reference centers and in developing countries. This technique is a new method controlled by a frequency meter and performed on stairs, which proved to be objective and reproducible for the diagnosis of CholU. As in other tests proposed in the

literature, all CholU patients showed characteristic signs and symptoms but not in healthy controls (4,14).

The method's sensitivity and specificity assessment presented robust values, mainly using two temperature measurement sites (forehead region and tympanic region). The values exceeded 80% sensitivity and 90% specificity, validating the method and providing reliability for its implementation in daily practice. However, measuring temperature in the oral region did not present statistically robust values, but the increase in temperature above the values of the control group was noticeable.

The method proved reproducible and bearable for the sample, as there were no interruptions during the test due to fatigue. However, going up and down stairs also presents itself as a limitation of the method, as patients suspected of CholU with risks inherent to the practice of physical activity or musculoskeletal limitations cannot perform the Provocation Test.

The average onset of signs and symptoms characteristic of CholU occurred at 19.5 minutes (10-30 min). In this study, the correlation within the studied sample between the moment of onset of the characteristic manifestations of CholU and severity was not evaluated. These parameters were assessed in another study (14) and demonstrated an inversely proportional correlation between the speed at which lesions appear and the severity of the disease.

The temperature of the Provocation Test environment was artificially controlled and varied between 20°C and 23°C. However, it is not possible to control only the relative air humidity; therefore, the partial results showed an average relative air humidity of 66% (58%-72%), characteristic of a tropical region with high rainfall levels such as Rio de Janeiro.

Many studies present a progressive increase in body temperature reaching 1°C as a direct correlation with the appearance of pruritic micropapular lesions associated with intense erythema in patients with CholU (4,14). However, the sample evaluated and presented in partial

results demonstrated lower values as an average variation above 0.5°C between the initial and final temperatures.

Thus, the results demonstrate the feasibility of reproducing the method and its consistency with the clinical findings characteristic of the disease. Therefore, it is expected that this simple and accessible method for diagnosing CholU can be a tool for application, mainly in developing countries, regions with difficulty obtaining high technological support, and the Public Health System. Therefore, it will assist in diagnosing a condition that is extremely harmful to the quality of life of the affected individual.

Conflict of Interest

S.D.J. declares he received lecture fees from AstraZeneca Brazil and G.S.K. Brasil. S.D.J. and S.V. declare they received lecture fees from Novartis Brazil. S.V. declared they received lecture fees from Takeda, Brazil. G.G.A. and A.T.F. have no conflicts of interest to declare. O.L. declares he received lecture fees from Sanofi Brasil. J.E.F. declares he received lecture fees from Sanofi Brasil, G.S.K. Brasil and AstraZeneca Brazil. Any authors have conflicts of interest with the specific topic of this article.

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Statement of Ethics

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Author Contributions

G.G.A. analyzed data, Investigation, Methodology, Project administration, drafted the manuscript, Resources, Software, Supervision, and Validation. S.D.J. and J.E.F. analyzed data, Investigation, and Methodology. A.T.F., O.L. and S.V. drafted the manuscript, Investigation, Methodology. All authors Validated and approved the final manuscript.

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Figure 1: Provocation test to CholU on stairs.



Figure 2: Showing average temperature variations between both groups

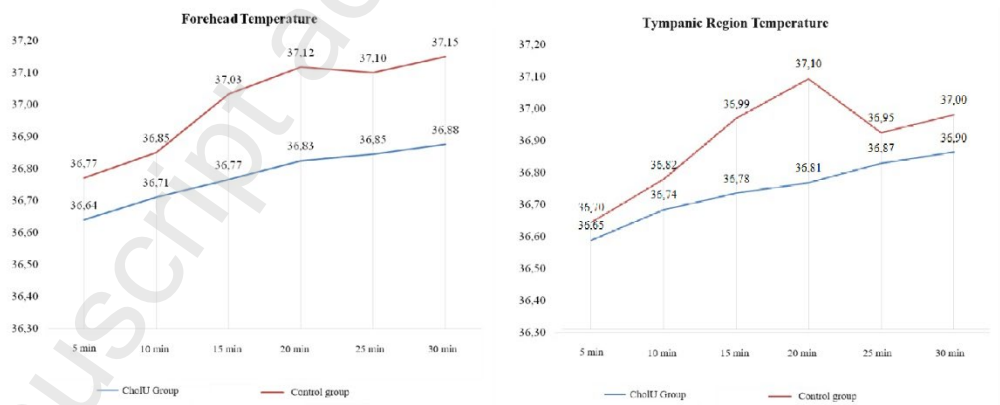


Figure 3: Flowchart to diagnostic Cholinergic Urticaria through Provocation test on stairs

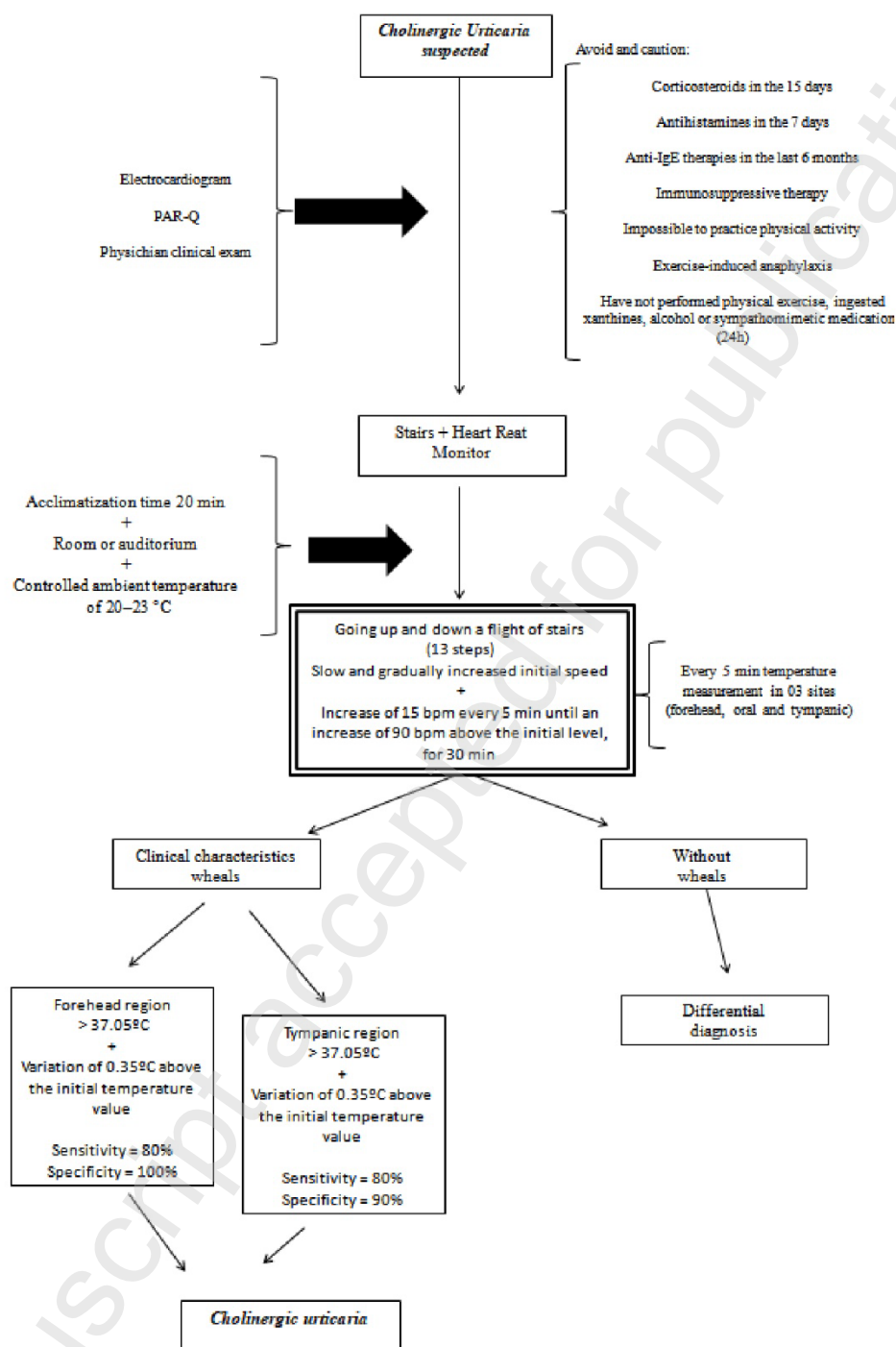


Figure 4: Cholinergic Urticaria during Provocation Test on stairs

