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Original Article

Regular sports exercises as a supportive therapeutic choice in cholinergic urticaria

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Abstract

Objective To emphasize the role of regular daily exercise as a possible supportive treatment for cholinergic urticaria, in addition to an oral antihistamine.

Methods Randomized cross-section comparative therapeutic study for 240 patients with cholinergic urticaria, screened from January 2021 to December 2022 at Dermatology and Venereology Private Clinic, Anbar, Iraq. A history was taken regarding the age, sex, onset and duration of illness, seasonal variation, presenting symptoms and signs, and time of the attack. Participants were randomly divided into 3 groups of 80 cases each. They were asked to complete a questionnaire of the urticaria activity score over 7 days- twice daily version. Only moderate to severe cholinergic urticaria were enrolled in this study.

Results The mean (range) age was 25.5 (18-45) years, 153 (63.8%) males and 87(36.2%) females. While 153 (63.8%) of patients presented in winter months. Generalized discomfort, acquired hypohidrosis, itching, and tingling were present in 234 (97.5%), 192 (80%), 177 (73.8%), and 63 (26.2%) individuals respectively. In comparison to each therapy alone, patients who used both oral levocetirizine 5mg/ day plus daily physical exercise for 30 minutes showed significantly marked improvement in 53(66.3%) of cases within 1st week, and 63(78.8%) of subjects at end of 2 weeks of therapy.

Conclusion Regular daily exercises plus H1 antagonists are beneficial for full recovery in the life quality for the majority of patients complaining of severe cholinergic urticaria. Generalized discomfort and acquired hypohidrosis are significantly correlating with disease existence.

Key words
Sports exercises; Cholinergic urticarial; Quality of life; Oral antihistamine; Acquired hypohidrosis.

Introduction

Cholinergic urticaria (CholU), was first defined by Duke in 1924. It characterizes by extremely itchy, or sometimes painful pinpoint wheals with neighboring erythema, usually occurring after sweating that is stimulated by rises in the body temperature, in response to hot showering, bodily exercise, and anxiety.[1,2] Although the symptoms usually diminish rapidly within 1 hour. But these feelings seem to disturb their life quality.[3]

The original mechanisms of CholU are not well understood. Patients with long-standing and severe disease complained of decreased sweating, and there is blockage of the sweat gland duct causing leakage of sweat antigens into the tissue leading to IgE-mediated mast cell stimulation.[4,5]

Many well-controlled clinical trials in the management of CholU showed that pharmacological treatments by antihistamines

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plus the avoidance of causative agents are the mainstays. But still had restricted effectiveness in severe conditions.[6] Little evidence showed that regular sweating activities and quick desensitization with sweat help treat CholU, especially in patients who resist conventional treatment and have sweat hypersensitivity.[7,8]

However, the present comparative study highlighted the role of regular daily exercise events as a possible potential helpful therapy for CholU, in addition to oral antihistamine intake.

Methods

Randomized cross-section comparative therapeutic study for 240 patients among 300 patients with cholinergic urticaria, screened from January 2021 to December 2022 at Dermatology and Venereology Private Clinic, Anbar, Iraq. This study was accepted by the University of Anbar, College of Medicine, Ethical Committee (Ref. No 26/April 22-2020). Obtained written informed consent from subjects after a full explanation of the nature of the disease and the treatment. Both genders older than 18 years were included in this study. Exclusion criteria included: Patients who showed ordinary urticarial symptoms or accompanying atopic disease, pregnancy, history of corticosteroids intake, and treatment of urticaria within the preceding 1 week.

The signs and symptoms of CholU were aggravated by heavy exercise using a bicycle treadmill or stair-stepping within 15 minutes including very itchy follicular, non-follicular 1-5 mm papules, wheals or erythema, located on the trunk and upper extremities that last for a few minutes to an hour.[9]

A history was taken regarding the age, sex, residence, occupation, onset and duration of illness, seasonal variation, presenting symptoms and signs: Itching or tingling unpleasant sensations, time of attack whether intermittent, day or nocturnal. Besides that, observed other accompanying CholU symptoms include acquired anhidrosis (hypohidrosis), anxiety, nausea, vomiting, hyperthermia, headache, and heat stroke.

At the first visit, all patients start oral placebo intake for 7 days, meantime they were asked to complete a questionnaire of the urticaria activity score over 7 days- twice daily version (UAS7TD) in the morning and evening, only moderate to intense CholU were enrolled in this study. Later on, UAS7TD repeated every 7 days **(Tables 1,2)**.[10,11] A daily UAS mark is obtained by adding the average daily itch severity score and average daily hives score (exacerbations that occurred during therapeutic exercise were excluded). In the present work, the surface area involved by pinpoint CholU, measured by the number of palms beside the duration of skin lesions at each attack, and called modified UAS. The weekly UAS7TD mark is gained by adding the daily modified UAS marks over 7 days. Scores were reported on the 7th of the first visit, and the 7th and 14th day after treatment. The UAS7TD marks range from 0 to 42, with higher

Table 1 Showing modified urticaria activity score, twice-daily form for CholU. [10,11]

Itch strength score	*Itch, tingling intensity at each check(am/pm)*	*Hives strength score*	*Number of hives at each check (or number of palms covers pinpoint hives)*	*Duration of skin lesions at attach*
0	No Pruritus or tingling	0	No hive	0
1	Mild, minimal alertness, simply tolerated	1	1–6	5–20 min
2	Moderate, definite alertness, troublesome but tolerable	2	7–12	20– 60 min
3	Severe, troublesome	3	>12	longer than 1 h

Table 2 Showing urticaria activity score over 7 days disease activity. [10,11]

Score	*Implication of urticaria*
0	Urticarial free- considered a full management response.
1–6	Good-controlled- indicates a good response to management.
7–15	Mild activity- indicates a lesser response level.
16–27	Moderate activity- standards for clinical trials.
28–42	Intense urticarial.

marks indicating higher activity. Subsequently, scoring was done later after two weeks of follow-ups to record possible relapse **(Table 1)**.

Participants were randomly divided into 3 groups of 80 cases for each, and they were advised to avoid ingesting hot or spicy diet and emotional stress.

Group A advised to take oral levocetirizine (5mg/ day), in the evening for 2 weeks. Without physical exercise.

Group B Treated with oral levocetirizine (5mg/ day), in the evening for 2 weeks. With daily physical exercise (using a bicycle treadmill or stair-stepping) for 30 minutes

Group C Patients were instructed to do daily physical exercise regularly (using a bicycle treadmill or stair-stepping) for 30 minutes for 2 weeks. Plus, oral placebo intake.

To avoid anaphylaxis and heatstroke during treatment. Participants in all groups were educated to take antihistamines and hydrocortisone injections on need. Also, they instructed to avoid rise in the body temperature, in response to hot water bathing, spicy food, and anxiety. On follow-up, the oral treatment stopped, while groups B& C continue on daily physical exercise only. Laboratory tests for a patient with urticaria are not required.[12]

By using SPSS version 22. Differences in proportions were compared. Statistical analysis of efficacy was completed by Chi-square test and Kruskal Wallis test. P values <0.01 were considered significant.

Results

Information from an entire 240 patients meeting inclusion criteria was presented for analysis. **Table 1** summarizes their characteristics. The mean (range) age was 25.5 (18-45) years, 153 (63.8%) males and 87(36.2%) females. Time of the season correlated significantly with the CholU where 153 (63.8%) of patients presented in winter months. The mean (range) recurrent number of CholU during life was 4 (1-16), and the mean (range) duration of skin lesions at the attack was 40 (20-90) minutes, and the bout significantly occurs at night in 130 (54.2%) of cases in comparison to day time in 82 (34.2%) of patients **(Table 3)**. The mean duration of illness in this research had 2 months (ranging between 1-6). The presenting and accompanying symptoms were generalized discomfort, acquired hypohidrosis, itching, and tingling in 234 (97.5%), 192 (80%), 177 (73.8%), and 63 (26.2%) individuals respectively **(Table 3)**.

According to the modified UAS7TD evaluation **(Figure 1)**, patients had scores of moderate and severe CholU participated in this research. Patients used oral levocetirizine 5mg/ day plus daily physical exercise for 30 minutes (group B) showed significantly marked improvement (CholU-free and good-controlled scores) occurred in 53(66.3%) of cases within 1st week and 63(78.8%) of subjects at end of 2 weeks of therapy. Whereas the therapeutic effects (CholU free and good-controlled scores) were non-significantly higher in group A than group C in 24(30.1%), 14(15.6%) of patients respectively at 1st week, and 20(25%), 14 (15.6%) of cases

Table 3 Showing baseline characteristics of patients' data with CholU, n=240.

Variables	*Data*
Age means (range)	25.5 (18-45) years
Sex	
Males N (%)	153 (63.8%)*
Females N (%)	87 (36.2%)
Season	
Winter	153 (63.8%)*
Spring	46(19.4%)
Summer	23 (9.6%)
Autumn	18 (7.5%)
Recurrence of CholU during life	4 (1-16)
Disease duration/weeks	8 (4-26) weeks
Duration of skin lesions at attack	40 (20-90) minutes
Symptoms	
Itching	177 (73.8%)*
Tingling	63 (26.2%)
Time of the day	
Nocturnal	130 (54.2%)*
Day	82 (34.2%)
Intermittent	28 (11.6%)
Accompanying symptoms	
Generalized discomfort	234 (97.5%)*
Acquired hypohidrosis	192 (80%)
Nausea, vomiting	12 (5%)
Headache	8(3.3%)

* Correlation is significant at P value <0.01

individually at 2nd week of treatment **(Figure1, Table 4)**.

After 2 weeks of follow-up, modified UAS7TD of group B revealed CholU-free and good-controlled scores in 76 (95.1%) of subjects, and it was significantly higher than in other groups 27 (33.8%) patients in group A and 23 (28.8%) cases in group C. The severe scores of CholU were significantly reduced in groups A and C (no patient) in comparison to their scores at the start of treatment in 28 (35%), and 31 (38.8%) cases respectively **(Table 4)**.

Similarly, during follow-up periods, 9(11.3%) cases in group A, and 22(27.5%) subjects in group C had moderate activity of the disease failed to treatment modalities. These marks decreased considerably in comparison to their scores at the time of enrolment in treatment, where moderate CholU reported in 52(65%), and 49 (61.3%) of cases in groups A &C individually **(Table 4)**. No patient established systemic wheal or anaphylaxis.

Table 4 Showing comparison of the clinical responses among groups according to modified UAS7TD.

Clinical response	*Score*	*Group A N= 80*	*Group B N= 80*	*Group C N= 80*	*p value*
(7^{th} day) before treatment					
Moderate activity	16–27	52(65%)	46(57.5%)	49(61.3%)	0.624
Intense urticaria	28–42	28(35%)	34(42.5%)	31(38.8%)	
(7th day) treatment					
Urticarial free	0	9(11.3%)	24(30.0%)*	3(3.8%)	
Good-controlled	1-6	15(18.8%)	29(36.3%)*	11(13.8%)	
Mild activity- a lesser response level	7–15	9(11.3%)	18(22.5%)	32(4%)	0.001
Moderate activity	16–27	34(42.5%)	3(3.8%) **	30(37.5%)	
Intense urticaria	28–42	13(16.3%)	3(3.8%) **	4(5%)	
(14^{th} day) treatment					
Urticarial free	0	0	35(43.8%)*	3(3.8%)	
Good-controlled	1-6	20(25%)	28(35%)*	11(13.8%)	
Mild activity- a lesser response level	7–15	44(55%)	13(16.3%) **	32(4%)	0.001
Moderate activity	16–27	16(20%)	2(2.5%) **	30(37.5%)	
Intense urticaria	28–42	0	1(1.3%)	4(5%)	
(14th day) follow up					
Urticarial free	0	0	39(48.8%)*	0	
Good-controlled	1-6	27(33.8%)	37(46.3%)*	23(28.8%)	
Mild activity- a lesser response level	7–15	44(55%)	2(2.5%)*	35(43.8%)	0.001
Moderate activity	16–27	9(11.3%)	2(2.5%)*	22(27.5%)	
Intense urticaria	28–42	0	0	0	

*P value <0.01 Positive correlation; **P value <0.01 Negative correlation

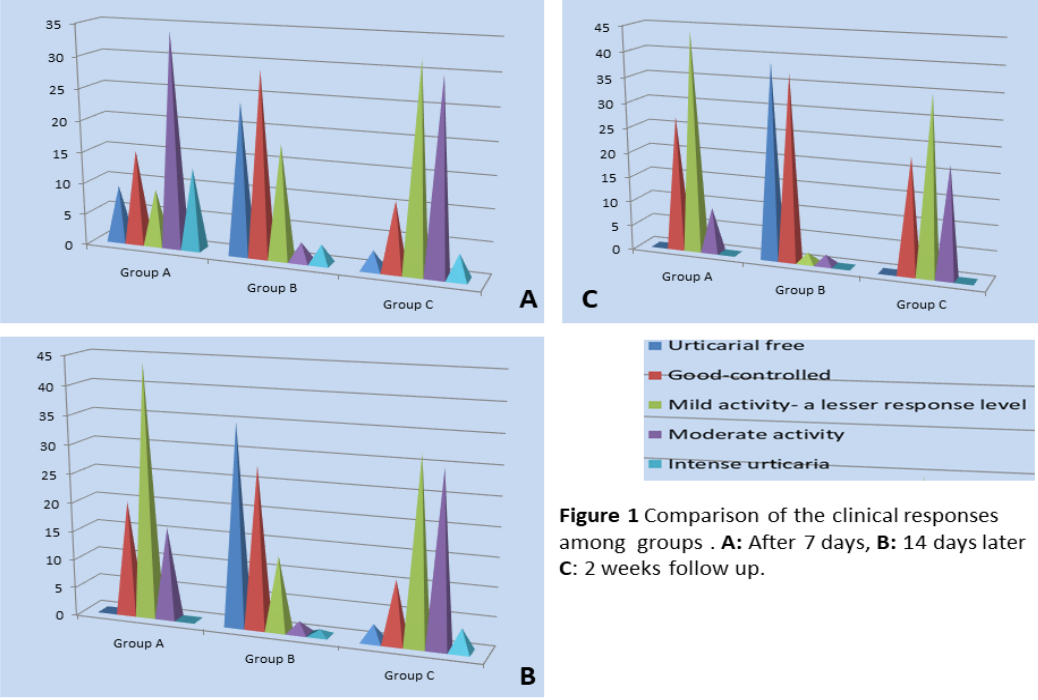

Figure 1 Comparison of the clinical responses among groups . **A:** After 7 days, **B:** 14 days later **C**: 2 weeks follow up.

Discussion

CholU is properly common, comprising about 30% of physical urticaria. The etiologies are a matter of controversy. Various causes of hypohidrosis or anhidrosis have been defined, including sweat glands dysfunction, sweat duct obstruction by keratin plug, and/or sympathetic nerve dysfunction, causing sweat filled with inflammatory substances to be refluxed into the dermis producing wheals.[7,13]

Disease involves young adults with mean (range) age was 25.5 (18-45) years. The mean (ranged) duration of illness during exacerbation was 2 (1- 6) months, and they experienced recurrence during life with a mean (range) of 4 (1-16) times. This is in line with past reports mentioned that the disease starts in puberty, but they found that the problem continues for years up to one or two decades before resolution.[14] Probably because the majority of participants included in this study group were those who change their daily habits and add various types of exercises like football, running and swimming. This leads to the remission of CholU for a long time.

The attacks of disease significantly occur at night in 54.2% of cases in comparison to day time 34.2% of patients. There are many explanations, maybe because the night has prolonged hours than the day, especially in winter months, could be related to an increase in body temperature during sleep, preceded by a hot bath, or sexual exercises. Besides that, the level of nocturnal cortisone is the lowest, making mast cells unstable.

Patients in this research using oral levocetirizine 5mg/ day plus daily physical exercise for 30 minutes (without systemic steroid) were significantly improved in the quality of life and CholU symptoms in 66.3% of cases within 1st week of therapy, 78.8% of subjects at end of 2 weeks, and 95.1% of patients at 2 weeks of follow-up.

Individuals enrolled with regular daily physical exercise using a bicycle treadmill or stair-stepping for 30 minutes showed non-significant beneficial control in 15.6% of patients at 1st and 2nd week of the study. Besides that, the severe CholU were significantly reduced in comparison to the condition before the enrolment in daily exercise.

Exercises using a bicycle treadmill or stair-stepping for 30 minutes, are fairly gentle and easy to achieve from the standpoints of the patient and the clinician. In ordinary life, many CholU patients avoid strenuous physical exercise. However, they were able to complete the protocol without undue discomfort. A previous study used physical exercise as a highly sensitive and specific provocation test for diagnosing CholU. This delivered an idea behind exercises as an add-on therapy.[15]

The last report revealed that sweating therapy by taking a warm bath, outdoor running or using an indoor treadmill for 10 minutes, 3 times per week alone or with an H1 antagonist or steroid oral pulse, gave relief of symptoms in 92% of the patients. But they used systemic steroids making the evaluation of this mode of treatment as an effective therapy difficult.[16]

Regular sweating and hardening could directly target the mast cells and make it inactive. Like what had been termed, "drug hypersensitivity and desensitization". Earlier works, using regular sweating therapy showed a reduction in the severity of the disease during the maximal outbreak.[1,17] After depletion of the content of the stimulated mast cell granules. Individual cells enter in early recovery and late recovery intervals that need from 3 to 48 hours.[18] In this work, regular daily exercise will interfere with full recovery and refill of mast cell contents and maintain a long duration of free CholU symptoms and histamine reduction. On the other hand, a recent study using lirentelimab in the treatment of CholU, a remedy that directly affected the function of mast cells, exhibited a good relief of symptoms in a majority of the cases.[19]

The present study is the first experiment to look at disease scores according to the number of hives measured by the number of palms covers pinpoint hives, offers evidence that pinpoint hives should be considered when studying the CholU. Palms numbers increase with disease progression.

The literature derived from Caucasian patients and Asian countries showed for the first time that hypohidrosis is a common feature.[20] In this study, acquired hypohidrosis was prevalent in 80% of individuals, and 63.8% of participants were men. The possible interpretations are the differences in sexual hormones could play a chief role in the pathogenesis of the disease, and the frequency of aggravating factors such as exercises in our society are more in men. Previous works presented higher female frequency, and gave an explanation that; generally, women seek specialized medical help.[14,21]

The obstruction of the sweat gland duct or sweat leakage into the tissue causes the induction of symptoms. Also, there is a decrease in the daily frequency of sweating in winter months, which makes the skin unfamiliar with the sweat antigens. This research found that winter months significantly affect 63.8% of CholU patients.

Studies reported that CholU aggravated in summer as sweating rises (23.0%) and those whose symptoms are exacerbated in winter (19.6%) as sweating declines. Moreover, other reports indicated that CholU was exacerbated only during winter, signifying an association between disease and low sweating levels, ductal

occlusion during diurnal activities, or even allergies to sweat secretion.[7,22,23] From this point of view, sweating therapy is thought as an important factor in those with CholU triggering in cold winter. Still, the mechanisms are unclear.

The clinical symptoms of CholU and the accompanying general symptoms were itching, and tingling, beside a generalized discomfort, and acquired hypohidrosis in 73.8%, 26.2%, 97.5%, and 80% of individuals respectively, and the mean (range) duration of the attack was 40 (20-90) minutes. This disagrees with a study in Korea that showed 91.3% of patients without associated general symptoms, and only 5.4% and 3.3% of patients had dizziness, and chest tightness separately.[9]

This research had limits, as skin morphology and the subjective symptoms were largely depending on the statement of participants by using the given chart of scoring.

Conclusion

Regular daily exercises cause skin hardening and regular sweating, in addition to H1 antagonists are beneficial in complete recovery in the symptoms and the life quality for majority of patients suffering severe cholinergic urticaria. Night times of winter are significantly correlating with disease occurrence. Generalized discomfort and acquired hypohidrosis are frequently associated with this type of physical urticaria.

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