Brief Report

Cyclosporine in Cholinergic Itch

Abstract

Cholinergic itch is part of symptom complex that also includes cholinergic erythema and cholinergic urticaria. It mostly occurs during the winters among young adults. It is characterized by onset of severe itching or burning sensation all over body, mostly, on exposure to sunlight, warm atmosphere and in some cases after hot and spicy food intake. In most of the cases, it is poorly responsive to anti-histamine therapy. **Materials and methods:** This was a prospective, open labeled, clinical study done in patients of cholinergic itch, refractory to both sedating and non sedating anti-histamine drugs, who attended dermatology clinic of our tertiary care center from November, 2020 to February, 2021. Oral cyclosporine was given as treatment. Numerical rating scale (NRS) was used to record the treatment response. **Results:** Twenty patients with cholinergic itch meeting inclusion criteria were included in the study. Mean age of disease onset was 19.5 years. Average duration of each episode was 4.4-8 minutes. More than one site was involved in all patients with trunk being the commonest (100%). There was significant reduction in the number of episodes and cholinergic itch severity (mean NRS=7.8 to 0.3 at the end of second week after initiating cyclosporine therapy). P value of the study was <0.0001. **Statistics:** Mean and standard deviation were used as measure of central tendency. Paired t test was applied to analyze the data obtained. **Conclusion:** Oral cyclosporine effectively controlled cholinergic itch in all included patients. Drug was well tolerated by the patients.

Keywords: *Anti-histamine therapy, Cholinergic itch, Cyclosporine*

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Introduction

Cholinergic itch is considered to be a part of the symptom complex that also includes cholinergic erythema and cholinergic urticaria. Cholinergic itch is characterized by sudden onset of severe itching, burning, or pricking sensations without any visible cutaneous changes. It primarily affects whole body in response to increased core body temperature, sunlight exposure, exercise/physical activities, warm atmosphere/clothing, emotional stress, and hot and spicy food intake.[1,2]There is a paucity of data related to management of cholinergic itch in the current literature, even though in some cases it can severely compromise the quality of life. In this report we have tried to assess the role of cyclosporine in severe cholinergic itch refractory to anti-histamine therapy.

Materials and methods

Twenty consenting patients of severe cholinergic itch refractory to both sedating and non-sedating antihistamine therapy were included in the study.

Itch severity before and after the treatment was assessed by unidimensional Numerical rating scale (NRS).[3]

Baseline blood pressure, baseline blood urea, serum creatinine, lipid profile, and liver enzymes were recorded and re-evaluated every 15th day.

Patients with poor or no response to both sedating and non-sedating antihistamine drugs (levocetirizine/chlorpheniramine maleate; given individually or in combination for 1 month) were administered oral cyclosporine (5mg/kg) for 2 weeks, and the dose was reduced by 50 mg every 15th day until a dose of 50mg/day was reached.

Inclusion criteria

Consenting patients of cholinergic itch not responding to both sedating and non-sedating antihistamine therapy.

Exclusion criteria

Patients with hypertension, deranged lipid, liver, and renal biochemical profile.

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Statistical methods

Paired t test was applied for NRS before and after the treatment. Clinical outcomes were found to be statistically significant.

Results

A total of 20 eligible patients were included in the study. The demographic profile of the patients is shown in [Table 1]. Cholinergic itch seems to occur predominantly in young males (M = 19, F = 1). Mean age of the included patients was 15.95 years. Mean age of the onset of disease was 19.5 years. Mean duration of the disease was 13.3 months. Cholinergic itch appears to occur more during winters as 13 (65%) patients reported either onset or recurrent occurrence of itch only during winters. In 8 (40%) patients, there was a history of atopic diathesis, but no active cutaneous manifestations of atopic diathesis (e.g., urticaria, dermatitis) were present. Mean NRS before initiating treatment was 7.8 which decreased to 0.3 at the end of the second week[Table 2 and Figure 1]. Eighteen patients (90%) reported the absence of any episode of cholinergic itch at the end of the first week of initiating cyclosporine therapy. The other two patients continued to develop cholinergic itch during the first 2 weeks with a significant decline in NRS score (initial mean NRS = 8.5 to NRS = 3). No episode of cholinergic itch occurred in any of the included patients after 2 weeks of starting cyclosporine therapy, even when the dose was tapered to as low as 50 mg/day over the period of 14 weeks. No post-treatment follow-up was performed.

Table 1: Demographic and clinical characteristics of cholinergic itch

Gender	
Male	19
Female	1
Mean age (in years)	15.95
Mean age at the onset (in years)	19.5
Duration (each episode in minutes)	4.4-8
Winter aggravation/onset	13
Spring aggravation	1
Summer aggravation	3
History of atopy	8
Aggravating/precipitating factors	
Sunlight exposure	19
Exercise	12
Hot food intake	2
Warm clothing	2
Emotional stress	3
Site of involvement	
Torso	20
Upper limbs	18
Scalp	17
Lower limbs	13

Discussion

Many patients of cholinergic itch do not reach clinics because of its transient, mild, and self-resolving nature that may not warrant treatment. However, some patients can be severely handicapped by episodes of intense pruritus that interferes with the daily activities or even forces a patient to avoid the triggers (e.g., exercise, warm clothing, field works). It is usually relieved by cooling the skin or in some cases taking the clothes off, which can be considerably embarrassing.

There have been few studies on cholinergic urticaria pertaining to its descriptive and management aspects,[4] but in general, there is a lack of such studies on cholinergic itch. However, in a recent case report, subcutaneous omalizumab was found to be effective in decreasing the severity of cholinergic itch.[5]

Lack of management guidelines and absence of any proven and effective drug therapies prompted us to carry out a study on management of cholinergic itch where it was severe enough for patients to seek medical advice, and the itch was non-responsive to both sedating and non-sedating antihistamine therapy.

Various mechanisms have been proposed which can explain the development of cholinergic itch and cholinergic urticaria symptom complex:

(A) Acetylcholine can act as endogenous algesiogenic in human skin as it produces burning pain sensations on intradermal injection[6] and as pruritogenic mediator in

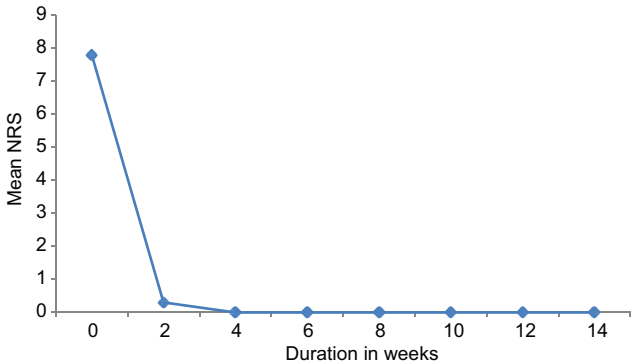

Figure 1: Mean NRS score decline with cyclosporine therapy

Table 2: Clinical response in terms of NRS

NRS at the start of the study	NRS at the end of the second week of starting cyclosporine therapy	NRS after 2 weeks till the end of the study	"*t*"	*P*=<0.0001
Mean±SD=7.80±1.10	Mean±SD=0.300±0.9787	NRS=0	22.72	

some skin diseases such as cholinergic urticaria and aquagenic pruritus.[7]

(B) Histamine also acts as an itch mediator, and its release can be stimulated by sweat-induced acetylcholine.[8]

(C) Xerosis induces sweat duct obstruction in winters, resulting in inflammatory substances contained in sweat being refluxed into the dermis.[7,9] Sweat materials contain numerous pruritogenic substances such as a renin-like substance, immunoglobulin E, secretory immunoglobulin A, and cytokines including interleukin 1/8/ß. Once leaked out from the sweat ducts, these may induce local inflammatory reactions.[10–13]

(D) Imbalance in cutaneous expression of several neuropeptides like substance P, vasoactive intestinal peptide, and neuropeptide Y is believed to be involved in the itch production in several skin diseases.[14]

Antihistamine drugs seem to work poorly in the cases of cholinergic itch and cholinergic urticaria; however, they are still considered as first-line treatment in cholinergic urticaria. Cyclosporine is known to produce anti-inflammatory and neuromodulatory actions.[15] Apart from anti-inflammatory action, it may also have anti-pruritic activity produced through neuromodulation by suppressing "pruritogenic cytokines" and by directly acting on cutaneous nerve endings, which leads to decreased levels of neuropeptide substance P, nerve growth factor, and neurotrophin-3.[16] It also decreases itch via interleukin-31RA inhibition and decreased TRPV1 and NKR1 gene expression.[15]

We chose cyclosporine as a therapeutic agent based on these various actions; many of these have been well demonstrated in its use in treatment of chronic spontaneous urticaria.

Conclusion

Oral cyclosporine appears to be very effective in decreasing the number of episodes and intensity of cholinergic itch within a very short duration of time (5–7 days). It can be considered as a short-duration alternative therapeutic option in patients of refractory severe cholinergic itch. However, as our study was for a limited duration, we could not conclude whether the symptoms would reappear once the patients are taken off the cyclosporine. Studies with larger sample size and longer follow-up period will be best suitable to further confirm the results observed and to determine for how long and in what dosage one can continue the cyclosporine in severe cholinergic itch.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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