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Danazol and Ketotifen in a Refractory Cholinergic Urticaria: Case Report

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Abstract

Cholinergic urticaria (ChU) is a type of induced urticaria characterized by small and pruritic wheals which are triggered by specific stimuli such as physical exercise thus significantly impairing the quality of life. The goal of treatment is to ensure prompt and prolonged control of symptoms, thus enabling the return to normal social activities. The traditional options are antihistamines, leukotriene inhibitors and immunosuppressive agents.

We present a case of refractory cholinergic urticaria who had an adequate response to danazol and ketotifen. Evaluating it by number of wheals, quality of life (Dermatology Life Quality Index (DLQI)), severity of pruritus (12-Item Pruritus Severity Score (12-PSS)) and pulse controlled, thereby proving to be an effective therapy in patients who don´t respond to conventional therapy and without access to biological treatment.

Keywords: Danazol; Ketotifen; Refractory cholinergic urticaria

Introduction

Urticaria is a disease manifests as wheals, angioedema or both. Approximately 50% of cases show both, 40% manifest only wheals and 10% only angioedema. Urticaria is categorized in acute urticaria and chronic urticaria. Chronic urticaria is classified as spontaneous or inducible. In inducible urticaria, hives result from exposure to specific triggers [1,2]. Cholinergic urticaria (ChU) is characterized by itchy, pinpoint-sized, evanescent wheals with large flare reactions triggered by exercise, passive warming, emotions and spicy foods, thus causing decrease in quality of life, especially in sexual interactions and the physical capacity.

The prevalence of this pathology varies from 0.2% to 11%, is more common in men, with an average onset age of 16 years [2].

The underlying pathogenesis of ChU are not well understood. Japanese studies suggest different phenotypes: (i) with poral occlusion (follicular type) (ii) with hypohidrosis; (iii) with sweat hypersensivity (non-follicular type); and (iv) idiopathic [3].

Acetylcholine, known to induce degranulation in mast cells, works also as a major messenger during sweat production. Various studies have shown that cholinergic agents induce sweat and the development of hives in patients with ChU. The "sweat hypersensitivity" hypothesis posits that patients who are hypersensitive to their sweat develop wheals in response to the release of sweat by the syringeal ducts in the dermis, possibly by obstruction of the ducts. Also acetylcholine may activate muscarinic CHRM3 on mast cells of sweat glands to cause wheals. Recent studies have demonstrated decreased expression of the muscarinic cholinergic receptor M3 and decreased expression of acetylcholine esterase in the skin of ChU patients, which suggest that cholinergic signaling pathways are relevant in ChU [3,4].

The treatment goal is to ensure rapid and persistent control of symptoms and therefore a quick return to normal social activities. The conventional treatment includes antihistamines, leukotriene inhibitors, and immunosuppressive agents. Ketotifen and Danazol may be helpful in patients with refractory cholinergic urticaria [5-9]. Omalizumab has been also reported successful in the treatment of refractory cholinergic urticaria in adults [5,6].

Rapid sweat desensitization with autologous sweat has been reported in patients resistant to conventional therapy who have sweat hypersensitivity [10].

Case Report

A 28-year-old Hispanic male with unremarkable past medical history (no atopy), presented with a 2-year history of exercise-associated rash. With even minimum workout he would develop extremely pruritic papules on his arms, which would quickly generalize and progress to respiratory distress and bronchospasm with a duration approximately of 30 minutes. Two months previously he experienced an increase in the symptoms, during which even light activity would induce the appearance of wheals, also noticing a decrease of sweat production. He denied the appearance of symptoms during hot baths, emotional stimuli or spicy foods. Numerous treatments (H1 antihistamines, beta blockers, steroids and bronchodilators) were attempted for several months without success. He is currently using only cetirizine in case of hives. Laboratory examinations showed an elevated total IgE levels of 244 kU/L. Skin-prick allergy testing was unremarkable with all specific allergen test negative. We confirmed ChU by a pulse-controlled ergometry test [11]. The test had to be canceled due to the rapid generalization of wheals after only 3 minutes of exercise without the presence of sweat (Figures 1 and 2).

With the diagnosis of refractory ChU and with biologic treatment wasn´t available, it was decided to start treatment with danazol (Novaprim) 100 mg/day and ketotifen (Nomotec) 4 mg/day. With significant improvement after 4 weeks, which was verified by the number of wheals, quality of life (Dermatology Life Quality Index (DLQI)), severity of pruritus (12-Item Pruritus Severity Score (12-PSS)) and by repeating the pulse controlled ergometry test (Table 1).

Now being able to finish the test, which was satisfactorily concluded after 30 minutes (Figure 3). During 6 months of use, the patient showed good tolerance with no side effects using both danazol and ketotifen, now being able to enjoy the activities of a normal life.

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Discussion

Physical urticaria is a unique subgroup of chronic urticaria and has a wide variety of triggers, including water, heat, cold, exercise, sunlight, pressure and vibration. Cholinergic urticaria is characterized by unique clinical features: pinpoint-sized highly pruritic wheals surrounded by erythema which occur after sweating while exercising (89%), strong emotions (60%), hot baths (80%), eating hot or spicy foods (29%) or raising body temperature. ChU patients predictably record the greatest disability by QOL scores and are the only urticarial group with limitations in sexual activities. Overall, prognosis is generally favorable, nonetheless 31% of patients have persistence of symptoms at 10 years with an average duration of 7.5. Even though symptoms and history are highly suggestable for ChU, confirmatory testing must be performed. Classically, an ID injection of 0.01 mg of methacholine in 0.1 mL of saline produces a local appearance of hives and is diagnostic of ChU. However, because only 1/3 of ChU patients show a positive test, it cannot be used to "rule out" ChU. Other tests may include exercise or hot water bath challenge. Under these conditions, the appearance of generalized urticaria confirms the diagnosis of ChU.

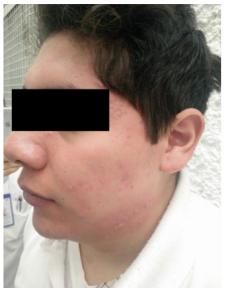

Figure 1: Patient after ergometry: Itchy single-pointed sized wheals due to the minimal physical exercise.

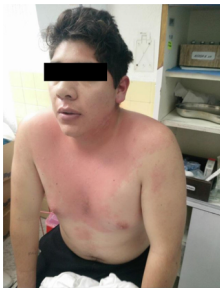

Figure 2: Patient after ergometry: The whole trunk is covered by itchy pinpoint-sized wheals with large surrounding flare reactions.

Figure 3: Patient after control ergometry: Pulse controlled ergometry test of cholinergic urticarial patient 4 week after danazol and ketotifen treatment. The patient developed , only pinpoint-sized wheals with almost no flare reactions.

Treatment	12-pss	Dlqi	Number hives (day)	Uas7	Pulse ergometry
Before treatment	20	19	6	28	The study suspended at 3 minutes by the appearance of generalized hives and nasal and eye symptoms
After treatment (4 weeks)	4	3	1	8	The test was tolerated up to 30 minutes presenting discrets hives 10 minutes after the study.
12-PSS: 12-Item Pruritus Severity Scale; DLQI: Dermatology Life Quality Index; UAS7: Urticaria Activity Score 7					

Table 1: Pulse controlled ergometry test.

Pathogenesis is not well understood. However, several studies suggest being mediated through acetylcholine and modifications in the muscarinic receptors giving place to the different suggested phenotypes of the disease. Those phenotypes may have a future place in the diagnosis and treatment perspectives.

Effective therapeutic approaches for the treatment of refractory cholinergic urticaria are not well established. Furthermore, treatment of refractory cholinergic urticaria with antihistamines is of limited success in most cases. This may suggest that histamine plays a minor role in its pathogenesis and additional mediators may be involved. Medical therapy is predominantly comprised of oral antihistamines, either H1- and/or H2-blockers, often at higher doses. Leukotriene inhibitors are often added to standard regimens. Oral anticholinergic agents have not shown efficacy.

Danazol, an attenuated androgen, has been used successfully in treating refractory ChU. Wong et al. did a double-blind placebo-controlled crossover study with 17 males with ChU. Danazol produced a significant decrease in wheal count, from 150 wheals after a standard exercise protocol to 39 wheals after 4 weeks of treatment. Ketotifen has also been shown to be effective in refractory cases. McClean et al. treated 4 cases of refractory cholinergic urticaria with 4-8 mg per day, having efficacy in 75% of cases. Kozaru and colleagues report the successful treatment of a ChU patient with partially purified sweat antigen immunotherapy.

Conclusion

In conclusion, the combination of danazol and ketotifen is effective in the treatment of refractory Cholinergic Urticaria. However, a future placebo-controlled clinical trial taking in consideration a higher population and the presence of a control group is warranted.

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