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Failure of omalizumab and successful control with ketotifen in a patient with vibratory angio-oedema

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Summary

Vibratory angio-oedema is a rare form of physical urticaria characterized by pruriginous weals and angio-oedema at the site of exposure to vibration. Severe treatment-resistant disease can occur, and is associated with significant disability. Therapy with omalizumab, a monoclonal IgG anti-IgE antibody, has been shown to be successful in several types of physical urticaria. We report a patient with vibratory angio-oedema for whom all standard treatments for urticaria, including omalizumab, failed to show a clinical benefit. Finally, ketotifen was tried, and unexpectedly reduced symptoms significantly. Ketotifen may thus represent a therapeutic option in patients with treatment-resistant vibratory angio-oedema.

Vibratory angio-oedema is a rare form of physical urticaria characterized by pruriginous erythemas at the site of skin exposure to vibration.[1] Typical stimuli include running, motorcycling, or using an electric lawnmower or pneumatic drill. Initially, this was described as an autosomal-dominant trait,[2] but sporadic cases also occur.[3] Avoidance of provoking stimuli may be associated with unacceptable impairment of daily activities. Symptomatic treatment of physical urticaria can be challenging, as the standard treatment with antihistamines often is unsatisfactory.[4] We report a patient with vibratory angio-oedema for whom all standard treatments for urticaria, including omalizumab were unsuccessful, but who showed a marked improvement with ketotifen.

Report

A 36-year-old white woman presented with a 20-year history of angio-oedema, with each episode lasting for several hours. Symptoms were always precipitated by exercise or vibration, such as running or fast walking, cycling on unpaved roads, hiking downhill or skiing on icy slopes, or even walking downstairs. The symptoms had become substantially worse during the previous few months, and were accompanied by dizziness, tachycardia and hypotension. There was no spontaneous urticaria.

On physical examination, there was no reaction to heat, cold or pressure, and the dermographic reaction was red.

Results of full blood count, erythrocyte sedimentation rate, electrolyte analysis and liver function tests were normal. Total IgE was 13 kU/L (normal < 120 kU/L). No histological examination was performed.

A treadmill test was performed at a constant workload of 6 km/h, and after 4 min of running, the patient developed angio-oedema on the buttocks. However, no elevation of serum tryptase levels before exercise (4.3 ng/mL), or at 30 min (4.5 ng/mL) and 2 h (3.6 ng/mL) after exercise was seen. Exercise testing on a bicycle did not produce any symptoms. A provocation test was performed using a laboratory vortex mixer running at 2400 rpm (Reax 2000; Heidolph, Schwabach, Germany); the patient rested her forearm on the mixer while it was run for periods of 5, 10, 20, 30, 45 and 60 s; any time period over 20 s was found to

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induce angio-oedema at the contact site around 5–10 min after provocation (Fig. 1a).

We started therapy according to current guidelines.[4] However, several different treatments [H1 blockers (cetirizine, fexofenadine, rupatadine; up to four times the usual dosage); combination therapy of H1 blockers plus montelukast and ranitidine; dapsone 200 mg/day; ciclosporin 200 mg/day; and methotrexate 15 mg subcutaneously per week] failed to produce any improvement, even though they were tried for several weeks in each instance. In addition, oral prednisolone 40 mg taken 1–12 h before provocation did not prevent symptoms. Therefore, after obtaining informed consent from the patient, we began off-label use of omalizumab 300 mg every 4 weeks. This was well tolerated for 3 months but was also ineffective with respect to both clinical symptoms and results of the provocation test (Fig. 1b). Finally, we decided to try mast-cell blockers; ketotifen 1–2 mg twice a day taken 1 day before physical activity produced a marked extension in toleration of the activities, and improved quality of life. Pretreatment prevented angio-oedema for most formerly non-tolerated activities (fast walking, cycling on unpaved roads, skiing on icy slopes, and slow walking downstairs). Only strong stimuli (e.g. fast walking downhill) still elicited symptoms. These beneficial effects were clearly reproducible, and symptoms immediately returned after ketotifen withdrawal. In the provocation test, noncontinuous on-demand pretreatment with ketotifen 1 mg twice daily before physical activity increased the weal threshold from 20 to 45 s. Of note, no significant sedative effect was seen.

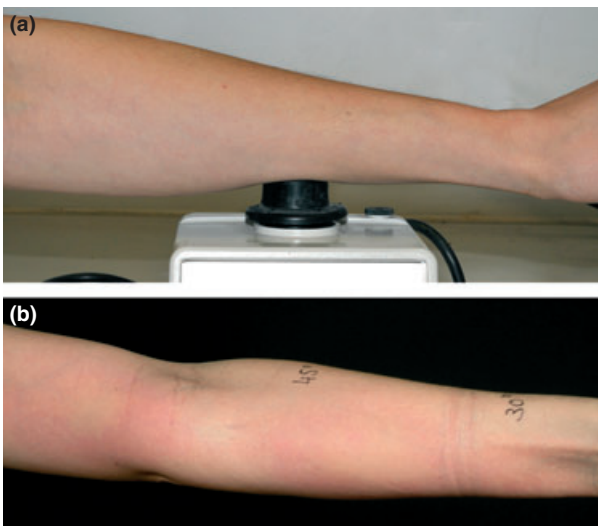


Figure 1 Vibration provocation test (a) patient's arm rests on laboratory vortex mixer set to maximum speed for 5–60 s; (b) strong angio-oedema occurred approximately 5 min after 30 and 45 s of vibration, even though the patient had received 3 months of treatment with omalizumab.

The pathogenesis of vibratory angio-oedema is poorly understood, and scientific evidence for effective treatment strategies is scarce. The primary aim is to control symptoms, which is most easily achieved by avoidance of provoking stimuli. However, this was impossible in our patient as symptoms also occurred during common daily activities, and severely affected her quality of life. Medical treatment follows the guideline recommendations for urticaria, starting with H_1 antihistamines as first-line treatment.[4]

In vibratory angio-oedema, evidence of mast-cell degranulation and increased levels of serum histamine during symptomatic episodes have been documented in some, but not in all cases.[3,5] Thus, treatment with H_1 antihistamines shows variable results. In our patient, second-line strategies, such as increasing the H_1 antihistamine dosage, addition of a leucotriene receptor antagonist, H_2 blockers, dapsone, ciclosporin and omalizumab, failed to produce any improvement.[4] A non-pharmacological approach (inducing tolerance by graded exposure to vibration) has been tried in a single case,[5] but was only partially successful, and a continued vibratory desensitization procedure was required. Omalizumab is of particular interest as it has been shown to rapidly induce complete resolution in many cases of chronic spontaneous or physical urticaria.[6–8] The mechanism of action of omalizumab in urticaria remains unknown, and does not correlate with IgE levels in patients. It has been speculated that a downregulation of IgE receptors on the surface of mast cells may lead to reduced release of mast-cell mediators in urticaria. However, it seems to be ineffective in vibratory angio-oedema, similar to findings in a recent case report on the use of omalizumab in cholinergic urticaria.[9]

Ketotifen is a sedating, noncompetitive cycloheptathiophene histamine antagonist, which inhibits the release of allergic mediators such as histamine, leucotrienes C4 and D4, and platelet-activating factor. It has been reported to be effective in some patients with a variety of physical urticarias, but the evidence has been rated as very low As its use is limited by its sedative effects, it is used only if treatment with other antihistamines fails. The effect of on-demand ketotifen in our patient is interesting, as in other patients it may become evident only after long-term regular use. This may point towards an effect on nonhistamine allergic mediators or receptors rather than on inhibition of histamine release. It is possible that the improvement in our single patient

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after ketotifen administration might be attributable to either a placebo effect or spontaneous remission; however, other, more powerful drugs did not produce such an improvement, and the patient's symptoms deteriorated after withdrawal of ketotifen, arguing against these possibilities.

In conclusion, although reports of the effect of omalizumab in urticaria are encouraging, more work is required to clarify which forms of angio-oedema are most likely to respond. This case indicates that in vibratory angio-oedema, the therapeutic effect of ketotifen might be superior to several of the more commonly used treatments, including omalizumab. Further research is warranted to shed more light on the pathophysiology of vibratory angio-oedema and to validate the effect of ketotifen vs. omalizumab in other patients with this disorder.

Learning points

- Vibratory angio-oedema is a rare form of physical urticaria, which may be severe and disabling.
- A standardized provocation test may be performed with the aid of a vortex mixer, on which the patient places their forearm.
- Medical treatment according to current guidelines may not be effective.
- In our patient, ketotifen, but not omalizumab, significantly attenuated symptoms, and should be included in the possible therapies for angio-oedema.

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