Special Article

Management of Chronic Idiopathic Urticaria

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Urticaria is characterized by wheals, which are superficial itchy swelling of the skin due to transient plasma leakage from small blood vessels. Angio-oedema occurs when the deeper dermis is affected. Urticaria and Angio-oedema can occur alone or in combination.

Appearance of wheals on a recurrent basis more than twice a week and lasting over 6 weeks is Chronic Urticaria. Wheals lasting less than 6 weeks is Acute Urticaria. Urticaria can also be episodic[1]. Chronc Urticaria can last from a few months to several years.

Acute Urticaria: Usually no tests are required for its evaluation. The treatment consists of H1 Anti histamine (oral/parenteral), steroids (oral/parenteral) and Adrenaline.

Episodic or Intermittent Urticaria: Here investigations for Type 1 Allergy (especially food allergens) may be useful. Skin prick test or RAST is done for the detection of allergens. Treatment is the same as in Acute Urticaria. Use of medication is as required.

Classification of Chronic Urticaria

1. Idiopathic - the great majori ty of CU is idiopathic. The probable aetiological agents may be Immune or Non-Immune[2]. The causative agent cannot be identified in most cases.

2. Physical - eg: Delayed pressure urticaria

3. Special types eg: Cholinergic urticaria

4. Diseases related to urticaria eg: Vasculitis

Probable causative agents in chronic Idiopathic urticaria[3] are-

1) Immune

(a) IgE dependent - This is seen rarely in Chronic Urticaria (though common in Acute and Episodic urticaria)

(b) Auto Immune - Constitutes one third of Idiopathic urticaria. Association with Hashimoto's thyroiditis is well documented.

2) Non-Immune

(a) Food pseudo allergens - Non IgE mediated hypersensitivity to food additives and some natural substances found in fruits , vegetables and spices.

(b) NSAIDs

(c) ACE Inhibitors

(d) Opioids

Role of Infections: Role of Helicobacter pylori and parasitic diseases has been proposed, but not proven[5,6.]

Psychological stress has also been postulated[3,7].

Investigations

A detailed clinical evaluation is found to be more useful than laboratory tests in the evaluation of chronic urticaria. In general laboratory tests are not useful[8]. However in some cases it may be possible to identify the aetiology as in Urticarial vasculitis. It may also help to identify any associated auto immune disorder. The tests indicated are:

1. Blood counts
2. ESR
3. Thyroid function tests
4. Serological tests
5. Skin biopsy

6. ASST (Autologous serum skin test)

7. Allergy tests

Estimation of C1 esterase inhibitor is useful only in angioedema without wheals.

Treatment

The ideal management of Chronic Urticaria would be identifying and eliminating the underlying causes and/or eliciting triggers. However this is not possible in the great majority of cases.

Role of Dietary management in Idiopathic urticaria[4]: In the case of Type 1 hypersensitivity, avoidance of triggering agent benefits within 48 hours. But this type is rare in Chronic Urticaria. In pseudo allergy, benefit will appear usually after 3 weeks of stopping the food. Diet with low pseudo allergens is advised in Chronic Urticaria.

The drugs used in the treatment of Chronic Urticaria are Antihistamines, Anti leukotrienes, Immuno suppressants and Omalizumab. Plasmapheresis is useful in Auto immune urticaria.

Antihistamines - The most effective treatment is symptom relief and antihistamines are the most important drugs in Chronic Urticaria.

Histamine is one of the key mediators released from mast cells and basophils[9]. It has an important role in allergic diseases including urticaria. Histamine1 (H1) receptor stimulation is responsible for most of the manifestations of urticaria namely, pruritus, vasodilation, vascular permeability, hypotension and flushing. Histamine2 (H2)receptor stimulation is involved in the manifestation of pruritus and flushing[10].

Antihistamines alleviate itching and reduce the number, size and duration of urticarial lesions. H1 activity in the afferent C nerve fibres cause itching which is mostly relieved by all antihistamines. Axonic reflexes of skin cause erythema. Receptors in the endothelium of post capillary venules cause extravasation (and wheal) formation. Anti inflammatory actions of Antihistamines are by two mechanisms:-1) Stabilization of mast cell and basophil cell membranes[11,12] and 2) Inhibition of cytoplasmic transcription factors[13].

Which Antihistamine to choose?

There are two groups of Antihistamines - the older sedating 1st generation antihistamines and the newer less (non) sedating 2ndgeneration antihistamines

1st generation antihistamines[14]: All drugs of this group are sedating. They are generally regarded safe by health care professionals because of their long standing use. But they decrease REM sleep, impair learning and work efficiency. They have been implicated in accidents (motor, aviation, boating). Deaths have been reported due to accidental overdosing in infants and adults. Intentional overdosing has also been reported in adult deaths. Some exhibit cardio toxicity in over dosage. Their duration of action is short. They have anti cholinergic side effects too.

The advantage of 1st generation antihistamines is that parenteral preparation is available which is useful in some cases of Acute Urticaria. If sedation is needed for insomnia in a patient with Chronic Urticaria, 1st generation antihistamines may be administered at bed time either alone or if necessary, along with a morning dose of 2nd generation antihistamines.

Hydroxyzine, Diphenhydramine, Chlorpheniramine and Promethazine are the drugs belonging to 1st generation antihistamines.

2ndgeneration antihistamines[15,16]: They are a heterogenous group of compounds. In contrast to the highly lipophilic nature of 1st generation antihistamines, the drugs belonging to 2nd generation antihistamines do not cross easily (if at all) through the bloodbrain barrier. Their propensity to occupy the H1 receptors in the CNS varies from 0% for fexofenadine to 30% for cetirizine (for 1st generation antihistamines it is 50-60%). Therefore these drugs are relatively free of sedating effects[17,18]. The duration of action is 24 hours or more.

Astemizole and Terfenadine were withdrawn because of cardiac toxicity. The currently available 2nd generation antihistamines are free from cardiac toxicity even at higher than recommended doses. None of these drugs are available in parenteral form because of their low aqueous solubility.

The drugs belonging to 2nd generation antihistamines are Cetirizine, Levocetirizine, Loratadine, Desloratadine,

Fexofenadine, Rupatidine, Ebastine, Acrivastine and Mizolastine.

Sedation of Fexofenadine and Desloratadine have been compared to placebo. Loratadine has mild sedation compared to placebo[19]. Cetirizine[20] and Levocetirizine were found to have more sedation than the above three drugs.

Combination of Antihistamines: Treatment with two or more drugs of 2ndgeneration antihistamines is not recommended. Instead, up dosing of 2ndgeneration antihistamines is preferred[21]. Also, combined use of 1st generation and 2nd generation antihistamines is not recommended. However, if insomnia is a problem, 1st generation antihistamines may be administered at bed time along with a morning dose of 2ndgeneration antihistamines.

H2 receptor blockers *:* If the patient is not responding to high doses of H1 antihistamines, then H2 antihistamines like famotidine or ranitidine may be given simultaneously. The combination of H1 and H2 antihistamines have been found to be effective in a subgroup of patients with chronic urticaria[27].

Steroids and Cyclosporine: Oral/topical steroids are not recommended in the long term management of chronic urticaria. Cyclosporine 3 mg/kg/day has better safety profile than systemic steroids[22,23]. But short course of oral steroids are indicated in acute or in episodic urticaria[24].

Drug treatment of Chronic Urticaria[21]

The step wise approach is -

1. 2ndgeneration antihistamines for 2 weeks
2. If not responding, 2nd generation antihistamines up dosing (2-4 times) for 1-4 weeks
3. If not responding, add Leukotriene antagonists and/ or change 2nd generation antihistaminesfor 1-4 weeks
4. Other drugs: H2receptor blockers, Cyclosporine, and Omalizumab may be tried in patients with chronic refractory urticaria.
5. Plasmapheresis in auto immune urticaria
6. Systemic steroids (3-7 days) in exacerbations.

Follow up - Re evaluate every 3-6 months as severity may fluctuate and the need for 2ndgeneration antihistamines may stop. Spontaneous remission is seen usually within one year though in some cases it may prolong.

Treatment of Chronic Urticaria in special situations[26]

Pregnancy: Cetirizine, Loratadine and Chlorpheniramine are in 'B' category whereas all other antihistamines are in 'C' category[25]. Avoid 1st generation antihistamines during the third trimester because of risk of neonatal seizures[14]. Safety of up dosing of 2ndgeneration antihistamines is not known.

Children*:* Same line of management as in adults is to be followed. 1st generation antihistamines should be discouraged in children. Liquid formulations of Cetirizine and Loratadine are available.

Liver diseases*:* 1st generation antihistamines and some 2ndgeneration antihistamines undergo metabolism in liver. Safest Antihistamines are Cetirizine, Levocetirizine, Fexofenadine and Desloratadine.

Renal failure: Cetirizine and Levocetirizine are to be avoided in severe renal failure.

Summary

Chronic Urticaria is a "difficult to manage disease." The main reason is that most of the times, a definite cause can not be identified. The most important point is that investigations are of limited use in this disease, nor does it help in the treatment. Moreover it unnecessarily increases the anxiety of patients. The cornerstone of medical therapy is antihistamines. The newer second generation antihistamines are preferred over the older first generation antihistamines. Up dosing of the former is recommended over use of a combination of two 2nd generation antihistamines.

In a minority of patients, where aetiology is identified, its elimination is the most successful treatment measure.

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