



### **Urticaria and angioedema**

Also known as hives or welts, this condition is characterized by development of red, raised, well circumscribed and very itchy skin lesions anywhere on the skin from daily to several times during the week. The size of the lesions can vary from small to large. They generally tend to be transient [less than 24 hours in duration] and do not leave behind any bruising or discoloration of the skin following resolution. By definition, hives lasting for longer than 6 weeks in duration are called chronic hives to be distinguished from acute hives which are of shorter duration. The hives can appear in conjunction with angioedema, or localized swelling of the skin, which predominantly affects the parts of the body where the skin is loosely attached such as the eyelids, lips, tongue, throat, voice box, gastrointestinal mucosa, hands and feet and genitalia. Unlike hives, which tend to itch, the angioedema causes discomfort, pain or burning sensation. Unlike generalized swelling resulting from heart failure, liver or kidney diseases, the localized angioedema tends to be unilateral [affects one side of the body and not both sides simultaneously]. They tend to last for 1-3 days. When the angioedema involves the throat or the voice box, this could result in difficulties in swallowing, talking or breathing. Emergency medical attention should be sought when this happens.

Both the hives and angioedema have similar mechanism of onset. In both conditions, the blood vessels in the skin get dilated, there is increased blood flow to the affected areas and there is leakage of fluid [and not blood] and later infiltration by inflammatory cells from the blood stream to the surrounding tissues. When the sequence occurs in the superficial layers of the skin, the hives result and when the same sequence occurs in the deeper layers of the skin, angioedema is the result. More serious disorders such as lupus and other connective tissue disorders cause inflammation of the blood vessels in the skin, which results in rupture of the blood vessels and bruising of the skin. When this happens, it takes several days for the bruise to resolve. The hives associated with connective tissue diseases in addition to causing bruising and lasting longer than hives from other causes, are often associated with other systemic symptoms such as joint pain, joint swelling, low-grade fever, sensitivity to sunlight, hair loss and ulcers in the mouth. If you notice any such symptoms in association with the hives, you should bring it to the attention of your doctor.

Acute hives could be secondary to allergy to foods, medications, insect bites, latex, radio contrast dyes, and contact allergy to several environmental allergens but

frequently, especially in children could follow a viral upper respiratory tract infection. The later condition is due to activation of the immune system which fights dead virus particles in the skin long after the virus is gone and this results in hives. It tends to resolve its self shortly. Physical factors such as excessive heat, sweating, exercise, mechanical pressure on the skin from tight clothes and weights, sunlight, vibration, extreme cold or even water could cause hives in



some people. Patient history is very important in elucidating this diagnosis. Usually no further testing is required. About 5% of normal people have a condition known as dermatographism. In this condition whenever the skin is stroked with a blunt object such as a tongue blade, there is formation of linear wheal and flare at the site of application of pressure. This condition could last for several years. Usually no further investigations are required. In 40% of patients with acute hives, an etiology(explanation) is found usually. In the remaining 60% an etiology may not be obvious. Most cases of acute hives resolve spontaneously or following removal of a known etiology.

Chronic hives are different. In greater than 95% of patients with chronic hives, there is no obvious identifiable cause. Even extensive investigations may not uncover a cause in such patients. In less than 5% of patients with chronic hives, food allergy plays a role. About 27% of patients with chronic hives have an associated thyroid dysfunction. It could be either hypothyroidism or hyperthyroidism. Many such patients also have an underlying autoimmune thyroid disease. In this condition, the body makes antibodies against its own thyroid tissue and slowly destroys the thyroid tissue over the years. Initially the disease could be asymptomatic and may not be discovered unless tested. Usually there is family history of thyroid disease. It is worthwhile investigating patients with chronic hives for the presence of autoimmune thyroid disease by checking for thyroid hormone level, TSH and thyroid autoantibodies. Adequate treatment of thyroid disease can often resolve the hives and angioedema.

For a long time it was not clear why autoimmune thyroid disease was associated with chronic hives. Within the last 10 years, there is evidence in the medical literature to show that such patients who have autoimmune thyroid disease and make thyroid antibodies also make autoimmune antibodies against IgE [human allergic antibody] or against IgE receptors, which are located on the mast cells. When these autoimmune antibodies combine with human IgE or with IgE receptors, the mast cells get simulated and release histamine and other chemical mediators of allergy and inflammation. This results in hives and angioedema. There is a test available to check for the presence of these autoimmune antibodies but this test is not widely available commercially.



The chronic hives and angioedema could last for several months or even years. Even though an etiology is not found, it does not mean those patients have to suffer for several years. There is a wide variety of treatment options available for patients with chronic hives and angioedema. Usually the chronic hives and angioedema are treated with antihistamines. There are two kinds of antihistamines: First generation antihistamines exemplified by Benadryl, Chlor-Trimeton, hydroxyzine, and cyproheptadine or second generation antihistamines exemplified by Claritin, Clarinex, Allegra or Zyrtec. The first generation antihistamines are usually more effective in controlling the hives and angioedema but they do cause sedation and tiredness. Therefore, patients may not like using them on a regular basis.

The second generation antihistamines are free of these side effects but are less effective. H2 blockers such as Zantac, Tagamet or Pepcid, which is usually used in the treatment of acid peptic disease of the stomach and esophagus, are also marginally beneficial in treating patients with chronic hives and angioedema. Singulair, a leukotriene antagonist has been found to be of no benefit or of little benefit in such patients. On the other hand, doxepin a widely used antidepressant is very effective in the treatment of chronic hives and angioedema. Like first generation antihistamines, it also causes significant sedation and tiredness and the patient compliance may be reduced for this reason. However it is important to know that the side effects of sedation and tiredness associated with first generation antihistamines and doxepin usually tend to get better with continued use of them as the body gets used to them. Patients, who take medications such as doxepin and first generation antihistamines should not drive, should avoid alcohol, and avoid using heavy machinery. Some states consider driving while taking these medications as a DUI violation.

It is our customary practice to start patients with chronic hives with non-sedating second-generation antihistamines. Sometimes a combination of these antihistamines is tried if a single agent alone is not helping. Addition of H2 blockers such as Zantac, Pepcid or Tagamet may also help some patients. If this strategy fails, we try using first generation antihistamines and or doxepin as a second line of treatment. Sometimes we need to titrate the doses of these medications until an adequate dose could be found that is both acceptable in terms of side effects and effective in alleviating symptoms. Steroids such as prednisone or Medrol Dosepak are very effective in controlling the hives and angioedema. However, prolonged use of these medications could lead to significant complications and side effects and therefore generally not recommended. There will be occasional patients who failed to respond to other treatment modalities and who may require the use of prednisone long-term. Other options should be exhausted

before resorting to this method and the risk versus benefit should be discussed with your doctor and clearly understood before agreeing to this modality of treatment.

Regardless of what treatment is chosen, it is very important that you comply with the treatment regularly. The hives and angioedema result from release of histamine and other chemical mediators from mast cells and other cells in the body. The antihistamines block the effect of histamine by combining with the histamine receptors in the skin and other places. The antihistamines cannot do this if the histamine is already combined with the receptor. The binding between histamine and the histamine receptor is irreversible. Moreover, new histamine receptors are made in the body every 24 hours. For these reasons, it is very important to take the medications daily as prescribed without skipping doses. For the same reason, these medications work better if taken daily rather than as needed.

In addition to medications, the following options also give relief in many patients with chronic hives and angioedema. This includes

- Avoiding excessive heat/sweating-by staying cool indoors, avoiding vigorous exercise and sports which makes one get hot and sweaty, taking tepid showers or baths instead of hot baths and keeping the inside temperature of the house at or below 75°F.
- Wearing loose fitting 100% cotton clothes and avoiding tight clothes such as tight jeans, brassieres and underclothing and avoiding wool and synthetic material such as nylon, polyester etc... Similarly, it is advisable not to cover oneself with lots of blankets while sleeping during the night.
- Avoiding alcohol which could aggravate hives
- Avoiding medications such as aspirin/NSAIDs [Aleve, ibuprofen, Excedrin, aspirin, Motrin, Advil, naproxen etc.] which tend to aggravate hives in 80% of patients when they are acutely suffering from hives and angioedema
- Avoiding other physical triggers such as excessive cold, sunlight, vibration or exposure to water where applicable and
- Minimizing stress if possible

Over-the-counter anti-itch medications such as Sarna anti-itch lotion may also be used on the skin several times to relieve itching. Over-the-counter hydrocortisone ointment and other prescription steroid creams may also be tried but prolonged application of them could result in bruising and excessive thinning of the skin, which could be permanent. Similarly, we do not recommend using Benadryl and doxepin on the skin as it may lead to sensitization and cause subsequent allergic reactions to these medications. However taking these medications orally is okay.



In women sometimes, the hives and angioedema tend to appear around menstruation and perimenopausal period. Hormonal influences are suspected in such patients but not proven. In some patients, the hives and angioedema could appear during later course of pregnancy and an autoimmune reaction against fetal tissue is suspected to be responsible for the occurrence of hives in such patients. The hives tend to get better after delivery. Steroids may be necessary to treat such patients.

There is a form of angioedema that tends to run in several family members. It is known as hereditary angioedema. It is due to absence or dysfunction of one of the proteins made by the body (c1 esterase inhibitor protein). In this condition, blunt trauma or surgery (including dental procedures) could initiate an episode. When the angioedema affects the throat or voice box, it could be life threatening. Sometimes the angioedema could involve the intestines and present as a surgical emergency such as appendicitis. Blood tests are available to diagnose this rare (1:50000 people are affected), but potentially serious condition. Family history is present only in 80% of patients suffering from the condition and in the remaining 20% the condition is suspected to be due to a new mutation. A new treatment option is available for this condition but is currently undergoing trials in the USA.