

REVIEW ARTICLE

DIAGNOSTIC AND THERAPEUTIC *ITER* IN CHRONIC URTICARIA PATIENTS

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We describe a diagnostic and therapeutic protocol for the management of chronic urticaria. It is derived from an extensive review of current literature, with a cost-effective evaluation of laboratory investigations and therapeutic approaches. Our protocol may not represent a cornerstone for chronic urticaria: much has in fact to be clarified on pathogenetic mechanisms and aetiological factors. Nevertheless, its application should be able, in our opinion, to identify what is useful or not in the everyday management of chronic urticaria patients.

Chronic urticaria, defined as lasting more than 6 weeks (1) often represents a diagnostic and therapeutic problem so that uniform behaviour in clinical management is needed (2). As hundreds of possible aetiological factors for chronic urticaria have been described (2-3), when the patient's clinical history is not helpful, most clinicians perform large scale diagnostic investigations (4-5). A critical evaluation of such extensive investigations has indeed shown that these are not usually able to provide a higher rate of aetiological diagnosis (6). This is partially due to weak or erroneous associations between chronic urticaria and many causative agents, which have been described in literature. Moreover, it is now clear that the identification of a trigger factor and its correction or elimination are often unable to control the clinical course of urticaria. (2, 7-9). This fact suggests that, in selected cases, the therapeutic approach interferes with a pathogenetic process, beyond the aetiological factor that triggered the urticarial reaction (10).

We propose a diagnostic and therapeutic protocol for chronic urticaria, based on an extensive review of current literature concerning chronic urticaria,

the prevalence of associated diseases, cost and effectiveness of each diagnostic procedure and data on the efficacy and safety of available drugs.

This protocol is intended for the prospective application on a chronic urticaria patient population aged 18-75, with the exception of pregnant women. As mentioned above, we define chronic urticaria as the presence of hives lasting more than 6 weeks (1, 11). A family history is the first step in providing important information and must be as accurate as possible. It may concern wheal characteristics, namely localisation, extension, persistence, evolution, presence of itch or pain, associated angioedema or other symptoms (anaphylactoid reactions, dyspnoea, gastrointestinal symptoms, arthralgias, fever, asthenia, lymphadenopathy, etc). Attention should then be addressed towards the identification of possible causative behaviours: it is important to rule out cases of physically-induced urticarias, such as cold, heat, pressure, radiation and cholinergic urticarias, and to perform a specific test for the suspected mechanism (cold test, water test and pressure test). The anamnesis must also investigate food intake, assumption of drugs and

Key words: chronic urticaria, diagnosis, treatment

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0394-6320 (2006)

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the presence of associated symptoms or diseases (especially regarding infectious, lymphoproliferative, neoplastic, thyroid or autoimmune diseases).

Physical examination

Clinical history should be completed in all patients with a standard physical examination, including vital signs, chest, neck, abdomen and lymph node evaluation and skin and mucous inspection.

Laboratory tests

If no possible aetiological factor has been identified with previous investigations, we propose to perform the following routine analysis: haemachrome, ESR, glycaemia, creatinine, transaminases, γ -glutamyltranspeptidases, alkaline phosphatase, lactic dehydrogenase, protein electrophoresis, anti-microsomal antibodies, thyroid stimulating hormone, antibodies to HIV, hepatitis B and C, PRIST, anti transglutaminase, IgA quantification, PRICK test for inhaled allergens (if suggested by clinical history) and RAST (if oral allergic syndrome is present). The aim of routine analysis should be a reasonable exclusion of significant haematological, liver, renal or endocrine diseases.

Additive-free diet according to Freedman and co-workers

This step is important for at least two reasons. Firstly, to evaluate the possibility of food intolerance caused by the accumulation of substances able to induce urticarial lesion without a classical IgE-mediated mechanism (vasoactive substances, molecules that can induce mastocytes degranulation, etc). Secondly, to evaluate the ability of this diet to reduce both the intensity of the symptoms and the need for antihistamines or corticosteroids, whatever the mechanism of chronic urticaria (12). If sulphite allergy or intolerance is suspected, then a sulphite-free diet should be administered.

In our opinion, if urticaria is still present after at least three weeks of an additive-free diet, and if clinical examination and laboratory investigations have not provided an aetiological diagnosis, then the clinician's behaviour should become more pragmatic and be addressed to treat the manifestation itself. To choose an adequate therapy it is important to distinguish between urticaria sustained by vasculitic

process and common urticarial lesions, without leucocytoclastic appearance in the histological analysis. Another important feature in chronic urticaria is an autoimmune mechanism in the aetiopathogenesis.

Skin biopsy should be performed by 4 mm punch (13). Light microscopy and direct immunofluorescence will evaluate the presence of leucocytoclasia and immunoglobulin/complement deposition. A mixed cellular infiltrate (lymphocyte, neutrophils and eosinophils) is the predominant feature of "common urticaria", while leucocytoclasia is the histological appearance of urticarial vasculitis.

Autologous Serum Skin Test (ASST) should be performed according to Sabroe (14). Briefly 0.05 ml of autologous serum should be intradermally injected on the volar side of the forearm with 0.05 ml of saline solution 0.9% as negative control. Results will be evaluated at 30'. In our diagnostic and therapeutic protocol the demonstration of leucocytoclasia and/or an ASST positive result would be a criterion for starting immunosuppressive therapy.

Therapeutic approach should be gradual, as follows: in patients showing a significant improvement or the disappearance of symptoms with the Freedman's diet, urticaria is related to food additive intolerance (6, 15). No provocation test with food additives should then be performed (16). These patients, after an adequate period (at least one month) of additive free intake, should undergo the reintroduction of the forbidden foods and the administration of anti H1 antihistamine drugs on demand. In patients showing no improvement with the additive-free food diet and no demonstration of a possible causative agent with family history, clinical evaluation, serological, haematological and instrumental tests, the therapeutic approach should be decided on the basis of the ASST and skin biopsy.

Presence of histological picture showing common urticaria and negative ASST

The first approach is the use of anti-H1 antihistamines for one month as they are the only registered drug for urticaria. If the patient is already taking antihistamines, it is possible to choose a different molecule of antiH1 (17). If urticarial lesions persist, an attempt should be

made with cinnarizine, a piperazine derivative able to control histamine release and to inhibit complement activation. In adults cinnarizine should be administrated at a starting dose of 25 mg tid. Anti-H1 antistamines should be administrated on demand and, if urticaria is heavily flaring, a short corticosteroid course can be associated (18). If unsuccessful, cinnarizine therapy should be replaced by anti-leukotriene receptor antagonists, namely montelukast, at a standard dose of 10 mg/die for three weeks. In the case of good clinical response, the drug should be continued for up to three months (19-20). Failure of these therapeutic approaches is an indication for immunosuppressive therapy, alone or in association with corticosteroids. Based on published evidence, out of all the immunosuppressive drugs we would choose to administer Ciclosporine-A (CyA) 5 mg/k/die (21-25).

Presence of a histological picture showing common urticaria and positive ASST

These features identify a heterogeneous group of patients, generally poorly responsive to H1 antihistamines drugs. For this reason we would choose to administer cinnarizine. The following steps do not differ from those above-described (montelukast followed by immunosuppressive therapy).

Presence of a histological picture showing urticarial vasculitis

These patients should be treated irrespective of the results of ASST. Cinnarizine associated to corticosteroids should be administered, the latter to be discontinued as soon as possible. NSAIDs should be administered in mild cases, especially if arthralgia-arthritis represents the only sign of systemic involvement. Published data identify indomethacin, at the dosage of 25 mg tid, as the most effective drug, (26-27). As a second-line drug we propose CyA, if no contraindications are present. Most authors agree with the dosage of 5 mg/k/die (28-29). If no adequate control is obtained, alternative immunosuppressive drugs (such as azathioprine or methotrexate) and/or IVIG and/or plasmapheresis should be considered (26-31).

CONCLUSION

Chronic urticaria is, in worldwide experiences, often difficult to treat. Antihistamine therapy, useful

in controlling pruritus, does not modify the expected duration of the disease. This represents a vexing problem for patients, because their quality of life is sometimes severely compromised. The application of the above-presented protocol should confirm or refute clinical usefulness of the chosen investigations and the ability of the proposed therapeutic approach in modifying the course of chronic urticaria.

We wish to point out that skin biopsy and ASST represent, in our opinion, an essential approach to chronic urticaria, able to classify patients in whom an immunosuppressive drug should be rapidly started and patients in whom a different therapeutic approach is more likely to be efficacious. We believe that the demonstration of leucocytoclasia and/or an ASST positive result is a criterion to start immunosuppressive therapy. This approach is due to the frequent systemic involvement in urticarial vasculitis, including vital organs such as kidney, brain and lung.

Regarding ASST, data from literature are not conclusive. A wide range of positivity for ASST (20-60%) has been reported in chronic urticaria patients (11, 14, 21, 32-33). It is generally agreed that an ASST positive result could be sustained by the presence of auto-antibodies, but must be kept in mind that also aspecific histamine release factors could be responsible for mast cell degranulation and wheal formation (34-35). Therefore ASST positivity is not a sufficient criterion to diagnose "autoimmune urticaria" while ASST negativity will always exclude an autoimmune chronic urticaria (11, 14, 32-33). Regarding its predictability on therapeutic outcome, some authors generally agree with a poor response to anti-H1 antihistamine drugs in ASST positive patients (36-37) and other authors outline that there is no relationship between ASST positivity and good CyA response (35, 38).

In our protocol, patients identified as having urticarial vasculitis or autoimmune urticaria, should be treated with CyA, the efficacy of which has been demonstrated since 1991 (21). Among immunosuppressive drugs it has shown to be the most efficient, both in chronic urticaria and urticarial vasculitis, due to its effects on pruritus (38), T lymphocytes (39-40), mast-cells and cytokines (41-42). The discontinuation of therapy with CyA is followed by a full relapse in about one-third of the cases; milder relapse is observed in another third

of the cases and a stable clinical remission in the remaining cases (37). We think that the proposed protocol will not confirm its usefulness in all the chosen steps but its wide application could allow to retrospectively identify what "is to be done" in chronic urticaria.

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