The Effectiveness of a History-Based Diagnostic Approach in Chronic Urticaria and Angioedema

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Objective: To assess the value of extensive laboratory screening for the identification of causes in patients with chronic urticaria and/or angioedema.

Design: In a prospective study involving 220 patients, 2 diagnostic strategies were compared: the combination of detailed history taking and limited laboratory investigations vs detailed history taking and extensive laboratory screening. The results of the extensive screening program were initially kept secret from the patients and the physicians. Later, all results were disclosed, and an investigation was undertaken to find out whether this information changed the initial diagnosis. The patients were followed up for 1 year to evaluate the results of interventions and to detect latent causes.

Setting: The study was performed in the outpatient department of a secondary and tertiary care center with institutional practice.

Patients: A total of 238 consecutive new patients with chronic urticaria and/or angioedema edema were referred; 18 of them refused participation. One patient was unavailable for follow-up.

Main Outcome Measure: The difference in the number of identified causes between both approaches and the nature of the causes that would have been missed by omitting extensive laboratory screening.

Results: With a questionnaire and the limited laboratory tests, a cause was found in 45.9% of the patients, compared with 52.7% with the questionnaire and the extended screening program. Except for one parasitic infection, missed diagnoses were mainly adverse reactions to drugs or food detected by standard elimination procedures, not by laboratory investigations.

Conclusion: Routine laboratory screening did not contribute substantially to the diagnosis of chronic urticaria or to the detection of underlying disorders.

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Approximately 12% to 24% of the population will have urticaria or angioedema at least once in their lifetime. In patients visiting general practitioners, an incidence of acute and chronic urticaria of 4.3 per 1000 patients and a prevalence of 5.0 per 1000 patients were reported; 5.1% of the patients had urticaria for more than 4 weeks, and 4.1% were referred to a dermatologist. In patients visiting dermatology outpatient departments, 1.4% to 2.4% had urticaria or angioedema. Urticaria can be intensely pruritic and may interfere with daily activities or sleep. Symptomatic treatment with antihistamines cannot completely suppress all symptoms in all patients.

Despite extensive (laboratory) investigations, 70% to 90% of chronic urticaria and/or angioedema remains idiopathic. In a subset (approximately 30%) of patients with chronic idiopathic urticaria, circulating IgG antibodies against the high-affinity IgE receptor (FcεRIα) were detected on mast cells. This recent finding, although a mechanism rather than a cause, is relevant to the pathogenesis of chronic urticaria and may have implications for future treatment. Still, in the majority of patients with chronic urticaria, neither a cause nor a mechanism can be discovered.

The sometimes poor response to symptomatic treatment and the inability of the physician to provide information on cause and prognosis are disappointing for the patients. Both patients and physicians may fear that the symptoms could be a manifestation of an underlying illness. Because of this fear, extensive and costly investigations are performed (eg, physical examinations, provocation tests, blood chemistry profiles, allergy tests, complement profiles, and screenings for infections, autoimmune diseases, etc.)
SUBJECTS AND METHODS

The study was designed as a per-patient comparison of 2 diagnostic strategies: a history-based diagnostic approach, consisting of detailed history-taking and a very limited set of laboratory tests, followed by additional tests only if necessary because of abnormal findings in the history, vs a routine approach, consisting of detailed history-taking and an extensive laboratory screening program. In the course of a prospective, protocolized study design, during which results from laboratory investigations became progressively available, dermatologists were asked to make a differential diagnosis on 2 successive occasions.

STUDY POPULATION

From January 1992 to July 1994, a total of 238 consecutive new patients who were older than 15 years, who had urticaria or angioedema for at least 6 weeks, and who consulted the outpatient Department of Dermatology were asked to participate. They received written and oral information about the purpose and special design of the study and gave their informed consent. Patients were excluded if diagnostic tests had already been performed (apart from the limited set listed below) or if their reference letter contained any information regarding possible causes. The Department of Dermatology of the Academic Medical Center at the University Hospital of Amsterdam in the Netherlands is a secondary and tertiary care center. The protocol was approved by the Medical Ethical Committee.

STUDY DESIGN AND FOLLOW-UP

A schematic representation of the study design is shown in Figure 1. Based on a questionnaire, which was filled in by all patients, and the results of a limited set of laboratory tests (determination of hemoglobin level, hematocrit, erythrocyte sedimentation rate, white blood cell count, and differential blood cell count), the dermatologist made a first differential diagnosis regarding the cause of the urticaria. Simultaneously, an extended diagnostic workup was performed by the investigators, but the results were kept secret. Additional laboratory tests could be requested by the dermatologist; all requests were recorded on the evaluation form. After 4 to 6 months, the remaining results were revealed to the dermatologist, and a second, sometimes revised, differential diagnosis was made. After a follow-up period of at least 1 year, each patient was reinterviewed and asked about any remaining or new complaints and, if indicated, laboratory investigations were repeated. The follow-up was necessary to detect causes initially not traced and to evaluate the results of interventions.

PATIENT QUESTIONNAIRE

A standard patient questionnaire containing 66 items was developed, based on earlier published questionnaires. The first part consisted of questions concerning frequency and pattern of attacks, duration of wheals, associated signs and symptoms, medical history, and general health (the questionnaire is available on request).

EXTENDED DIAGNOSTIC WORKUP

The extensive laboratory investigations included hemoglobin level, hematocrit; erythrocyte sedimentation rate; and malignancies). Large clinical studies have shown that the frequency of severe underlying diseases in patients with urticaria is low. In the literature, it has been suggested that too much time and money are spent on routine investigations and that more time should be spent on history-taking. Despite these recommendations, extensive routine screening procedures are still widely used. In this time of evidence-based medicine, the only way to change this attitude would be to provide the evidence that extensive screening is unnecessary. To achieve this, we prospectively investigated the additional diagnostic value of extensive laboratory screening. The aim of this study was to investigate the hypothesis that when the patient's history is recorded thoroughly, extensive laboratory screening does not substantially disclose more causative factors than does the limited set of laboratory tests.

RESULTS

PATIENT POPULATION CHARACTERISTICS

A total of 238 patients with urticaria were referred to the outpatient department. Eighteen patients refused participation. Seventy-four percent of the patients were referred by a general practitioner (13% of the 74% represented requests for a second opinion); 19% of the patients were referred by a dermatologist; and 7% were referred by other specialists. There were 132 women and 88 men; the mean age was 37.5 (age range, 15-79) years. The median duration of their urticaria and/or angioedema at inclusion was 15 months. The distribution of the duration in our patient population is shown in Figure 2.

ASSOCIATED SYMPTOMS AND PATIENT HISTORY

Associated symptoms during attacks of urticaria or angioedema were dyspnea (13%), hoarseness (9%), and a swollen tongue or throat (7%). Five patients reported severe anaphylactic reactions. The following complaints related to the atopic syndrome were reported by 40% of the patients: atopic dermatitis (5%), asthma (15%), allergic rhinitis (17%), and conjunctivitis (18%). Forty patients (21%) reported a history of adverse drug reactions, and 60 patients (31%) suspected a particular food as the cause of the urticaria.
white blood cell count; differential blood cell count; total eosinophil count; liver and kidney function tests; determination of levels of glucose, protein, complements, circulating immune complexes, and cryoglobulin; serologic tests for rheumatoid factor, IgE and antinuclear antibodies; hepatitis B. syphilis, antistreptolysin titer, Strongylodes, and anti–double-stranded DNA; and radiolabeled haptens (RASTs) for inhalation allergens (mixtures of rodents, birds, fungi, grass pollen, birch pollen, mugwort pollen, cat dander, dog dander, and house dust mites), food allergens (mixtures of crustaceans, fish, meat, wheat, fruits, vegetables, soy, peanuts, and peas), and other allergens if suspected. Urinalysis and examination of stools for parasites and occult blood were performed. Smears from the throat were cultured for streptococci, and smears from the vagina were investigated for Candida organisms. Radiographs of the chest, paranasal sinuses, and teeth were obtained to search for possible infections or malignancies. Skin biopsy specimens were obtained from urticarial lesions. Each patient was given a routine physical examination and provocation tests for physical urticarias as described by Henz et al (dermatographism and cold urticaria). Other physical provocation tests were performed when deemed necessary. If the patient used drugs, a determination was made as to whether there was a possible time relationship with the urticaria, and treatment with all drugs was discontinued or replaced with chemically unrelated equivalents. Suspected underlying diseases were treated whenever possible to find out whether there was an association with chronic urticaria. An elimination diet (ie, a diet without salicylates, dyes, benzoates, sorbic acid, sodium glutamate, sulfites, antioxidants, sodium nitrate, parabens, vasoactive amines, histamine liberators, sugar, yeast, spices, coffee, crustaceans, fish, meat, eggs, milk products, and potatoes) was prescribed for at least 3 weeks to screen for adverse reactions to food. Drug provocation tests and oral food rechallenge tests were performed when necessary.

SAFETY AND EXPERT COMMITTEES

A safety committee examined the results from the extended diagnostic workup when they became available to check for abnormal values that would require immediate intervention. An expert committee also tried to discern the most likely cause(s) of the urticaria in each patient, initially based only on the history and findings of limited laboratory tests, later based on all the available information. The (differential) diagnosis of the expert committee was not disclosed to the dermatologist to avoid bias due to a “learning effect.”

ANALYSIS

The effectiveness of the history-based diagnostic approach (Table) was assessed by comparing the number of causes identified correctly by the dermatologists in their first differential diagnosis (based on limited laboratory tests) with the number of causes in their second differential diagnosis (based on the extended diagnostic workup). The first and second differential diagnoses of the dermatologists were compared with the final expert diagnosis, defined as the most likely cause of the urticaria. A diagnosis was considered correctly identified if the final expert diagnosis was mentioned on the evaluation form as the possible cause of the urticaria.

Also, for each individual patient, an analysis was performed to determine whether a cause that was identified by the expert committee was missed by the dermatologists and whether this oversight could have been avoided by the use of routine laboratory tests, provocation tests, or any other diagnostic procedure.

FIRST DIAGNOSIS OF THE DERMATOLOGISTS

Up to 5 suspected diagnoses could be recorded on the first evaluation form by the dermatologists; the mean number of recorded diagnoses was 2.3 per patient. The most frequent diagnoses were physical urticarias (182), unknown cause (111), infection (50), adverse reaction to food (44) or drugs (43), inhalation allergens (40), and internal diseases (22).

In 33 patients (15%) no additional investigations were requested and in 150 patients (68%) fewer than 5 investigations were requested by the dermatologists on the first evaluation form. The most frequently requested additional investigations were determinations of IgE antibody levels and RASTs for inhalation allergens (81), RASTs for food allergens (34), and an elimination diet (30).

EXTENDED DIAGNOSTIC WORKUP AND FOLLOW-UP

The safety committee did not observe any serious abnormal test result that would have required an immediate intervention. Clinically relevant abnormalities of

**Figure 1.** Summary of study design. In all patients, extensive screening took place at the first visit, but the results were kept secret for the treating dermatologists. Only a safety committee saw the results to check for abnormal values that would require immediate intervention. Both the dermatologists and an expert committee made a first diagnosis on the basis of a detailed questionnaire and a very limited set of laboratory results. Four to 6 months later, all results were revealed and an analysis of how this additional information influenced the diagnosis was performed. The final, most likely diagnosis was made by the expert committee on the basis of all available information after 1 year of follow-up. Hb indicates hemoglobin; Ht, hematocrit; ESR, erythrocyte sedimentation rate; and DCC, differential cell count.
the erythrocyte sedimentation rate were found in 20 patients. In 4 patients, this abnormality could be related to an internal disease (Sjögren syndrome, systemic lupus erythematosus [SLE], paraproteinemia, or mesothelioma). Twenty-three patients had a decreased level of C4 (<0.2 g/L), including the patients with Sjögren syndrome and SLE. Circulating immune complexes (C1q-binding test >14%) were found in 17 patients, including the patients with Sjögren syndrome, SLE, and paraproteinemia.

The levels of serum IgE were elevated in 20 patients: 500 to 1000 kIU/L in 8 patients and 1000 to 2000 kIU/L in 12 patients. Antibodies (RASTs) to inhalation allergens were present in 69 patients and to food allergens in 19 patients. These antibodies could be related to the development of urticaria in 6 patients. Infections such as vaginitis (26 patients) and cystitis (18 patients) and elevated antistreptolysin titers (42 patients) were found, but treatment did not resolve the urticaria. Occasionally, the results of the other laboratory tests were abnormal, but the abnormalities were not clinically relevant to urticaria. The mean follow-up period was 21 months (range, 12-48 months). One patient died of mesothelioma 25 months after the first visit. He had urticaria due to an adverse drug reaction.32 Only the 4 patients mentioned above developed an internal disease or malignancy. During the follow-up period, 6 patients became unemployed because of severe daily complaints. One patient was unavailable for follow-up.

**FINAL EXPERT DIAGNOSIS**

The final expert diagnosis was based on the questionnaire, results of the extended diagnostic workup, and all the information obtained during the follow-up period. Sixty patients (33.2%) had urticaria or angioedema due to physical stimuli such as pressure, cold, heat, or light. Twenty patients (11.4%) had a combination of physical- and idiopathic urticaria (Table). In 10 patients (9.1%), adverse drug reactions were identified as the cause of urticaria. The symptoms recurred in all patients after rechallenge with the suspected drugs, and in every case, the urticaria was cured by permanent elimination of the drug use.

Fifteen patients (6.8%) had adverse food reactions; nine of them had already suspected food as the possible cause. Two patients with adverse food reactions had exercise-induced food-dependent reactions. Ten patients had a parasitic infection without diarrhea. Eight of the 10 patients had been born in a tropical country, and 2 had worked in one for more than 1 year. Six of the 10 had eosinophilia. In 4 patients, treatment of the parasitic infection resulted in the disappearance of the urticaria. In these 4 patients, the infection was considered to be related to the urticaria. In 3 patients, an internal disease was found that could be related to urticaria (ie, Sjögren syndrome, SLE, and paraproteinemia).

In 46.9% of the patients, the cause of the urticaria remained unclear. The patients with physical and idiopathic urticaria were classified as having idiopathic urticaria because most of them considered it their most important complaint. The physical urticarias could be
were found in other studies. Of course, we cannot guarantee that the final cause identified by the expert committee is correct in all cases. It is the most likely cause to the best of our knowledge. The expert committee consisted of the primary investigator and 2 staff members with more than 10 years of experience with chronic urticaria. After detailed examination of all laboratory test results and all other information in each patient’s file, the committee members made their diagnosis without time constraints after 1 year of follow-up.

The dermatologists missed 9 adverse drug reactions, which could have been detected if treatment with all suspected drugs had routinely been discontinued. The pressure urticaria that was missed in 4 patients could have been found if the questionnaire had been read more carefully. The parasitic infection would not have been missed if a search for parasitic infections had been done in all patients who had lived or worked in tropical countries. Adverse food reactions were highly overestimated as a cause of urticaria by the patients (31%) and the dermatologists (20%). Therefore, determination of IgE levels and RAST results were requested. The results of the RAST for food allergens was relevant in finding the cause of the urticaria in only 15 patients (6.8%). On the other hand, six adverse food reactions were missed by the dermatologists and 5 were missed by the expert committee as well because thorough history taking did not reveal them. The adverse food reactions were found with an elimination diet. As a last effort, such a diet could be advised for some motivated patients, even with no indication of an adverse food reaction in the history.

In 3 patients, the most probable cause of the urticaria was an internal disease (ie, Sjogren syndrome, SLE, and paraproteinemia). After treatment, the urticaria diminished, but this improvement could also be related to the treatment itself. Because of associated symptoms mentioned in the questionnaire (eg, joint pain or malaise) or because of an elevated erythrocyte sedimentation rate, the dermatologists requested further laboratory tests and therefore the diseases were not missed. One patient with idiopathic urticaria developed Raynaud phenomenon after 1 year of follow-up. No other complaints or laboratory results indicating an autoimmune disorder were present during 3 years of follow-up.

In our study, no malignancy related to urticaria was found, but the number of enrolled patients was too small in relation to the low incidence of malignancies in chronic urticaria to provide reasonable security that no underlying malignancy would be missed by using this approach. In patients with lymphoproliferative disorders, a prevalence of 0.5% of symptomatic, acquired, Cl-inhibitor deficiency presenting as angioedema was observed. The relationship between urticaria and malignancies was analyzed in a prospective 10-year follow-up study of 6913 allergic adults. The relative risk of leukemia, lymphoma, or myeloma developing in patients with a history of hives was 7.89 (confidence interval, 3.13-19.89). Although the relative risk of malignancies is high in patients presenting with urticaria or angioedema, the absolute risk is very low. Therefore, we believe that there is no reason for routine screening without any indication of an underlying malignancy.

Although there is an evident trend to reduce laboratory investigations in patients with chronic urticaria, extensive investigations are still recommended in textbooks and reviews. performed in clinical trials, and carried out by many physicians. One of the reasons for requesting extensive investigations is that some patients request them because they fear that their hives

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**EFFECTIVENESS OF THE HISTORY-BASED DIAGNOSTIC APPROACH**

To measure effectiveness, the first and the second differential diagnoses of the dermatologists were compared. This comparison represents the actual circumstances in daily clinical practice, with the potential differences in knowledge of the different dermatologists and the time pressures in an outpatient department. The overall effectiveness was 87% (Table). Nine adverse drug reactions and 6 adverse food reactions were missed. In 3 of the 6 cases, the patient’s history revealed no information regarding adverse food reactions. In 4 patients with physical and idiopathic urticaria, pressure urticaria was not mentioned as a possible cause. One parasitic infection was missed.

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**COMMENT**

This study demonstrated that an extended diagnostic workup (extensive laboratory screening, routine physical examination, and routine physical provocation tests) is not necessary in patients with chronic urticaria or angioedema if thorough history-taking is performed. Nineteen of the 20 missed diagnoses could not have been found with routine laboratory tests. In only 1 patient with a parasitic infection, which was not suspected by the dermatologist, could routine screening have contributed to the diagnosis. No severe underlying diseases were missed.

A limitation inherent to the study design is that the study was performed in a secondary and tertiary care institution and that the results may not be applicable to other types of clinical settings. In our study, 61% of the patients were directly referred by their general practitioner. It is conceivable that during the investigation the dermatologists were more precise in history taking because they knew that their diagnoses were going to be recorded. On the other hand, it is possible that some of them were less precise because they knew that all patients were going to be thoroughly evaluated by the expert committee.

The expert committee was able to identify the cause of the urticaria in 53% of the patients. The percentage of identified causes is high compared with those of other patient series, probably because a considerable percentage (33%) of physical urticaria cases were detected through standard provocation procedures. The diagnosis of physical urticaria was made only if the physical factor was the patient’s main problem. Similar percentages of physical urticaria cases and combination physical and idiopathic urticaria cases were found in other studies. Of course, we cannot guarantee that the final cause identified by the expert committee is correct in all cases. It is the most likely cause to the best of our knowledge. The expert committee consisted of the primary investigator and 2 staff members with more than 10 years of experience with chronic urticaria. After detailed examination of all laboratory test results and all other information in each
are caused by an underlying disease and they want to be reassured. Also, the fear of legal claims force physicians to perform extensive investigations to make sure that no known underlying cause is overlooked. Performing endless screening series owing to the fear of “failure to diagnose” leads to increasing costs and frustration on the part of both the patient and the physician. According to the principles of evidence-based medicine, diagnostic tests that do not contribute to the diagnostic process should not be performed.\(^3\),\(^3\) Whether a diagnostic test is useful or not depends on how the outcome of the test can change the pretest probability of a certain underlying disease or causative factor.\(^3\),\(^3\) In chronic urticaria, only a few specific laboratory tests, such as the dermatographism test for urticaria factitia, appeared to be valuable in this respect.

The history itself can be regarded as the most valuable diagnostic tool. Each item of the history can be considered as a diagnostic test that either increases or decreases the probability of a target disorder.\(^3\) By combining several questions, the probability that certain underlying diseases or factors are present can be reduced to nearly zero or nearly 100%. In both situations, additional laboratory tests are not necessary.

With the history-based approach, the dermatologists requested fewer laboratory investigations and felt more secure that they did not miss underlying diseases. As a consequence of this study, we no longer perform routine screening investigations in patients with chronic urticaria.

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