

POSITION PAPER: CONTROVERSIAL AND UNPROVEN DIAGNOSTIC PROCEDURES FOR FOOD ALLERGY

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INTRODUCTION

As a matter of fact, allergic diseases are constantly increasing worldwide (1). The large population-based epidemiological studies indicated that, at least in westernized countries, the prevalence of allergic diseases approaches 30% of the general population (2-4). Nevertheless, in everyday life, the apparent prevalence of allergic diseases is further overestimated. One of the reasons is the incorrect use (even among physicians) of the term "allergic", so that also toxic reactions or side effects of drugs are classified as allergic. Another reason is that many heterogeneous clinical syndromes (including migraine, irritable bowel, chronic fatigue syndrome, hyperkinetic syndrome, seronegative arthritis, otitis media) are often considered as allergic, despite no formal demonstration has been so far provided (5). In this regard, it is well known that "food allergy" is often considered as a simple pathogenic explanation of those symptoms which cannot be clearly classified. This fact is well exemplified by the results of two studies (6, 7) which compared in a general population the prevalence of food allergy suspected by patients with the results of the double blind placebo controlled food challenge (DBPCFC) (table 1).

D. Altman, L.T. Chiaramonte (1994) 1483 patients	12,4 %	0,8 %
JO'B. Hourihane (1994) 7500 patients	19,9 %	1,8 %

Table 1.

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There are some possible explanations for the discrepancy between the clinical aspects and the results of the DBPCFC, such as the poor reliability and reproducibility of skin tests with fresh food (8), and the overlap of different pathogenic mechanisms (9). Nevertheless, the aforementioned results prompt us to meditate on the problem of diagnosing food allergies/intolerances.

In the case of adverse reactions to foods, due to the confounding clinical aspects and the incomplete knowledge of the mechanisms (10), the alternative or unconventional diagnostic techniques are largely applied. Alternative tests are appealing because they are usually non-invasive, provide quick answers, and integrate different kinds of approach to diseases.

Due to the large diffusion of alternative approaches, the high prevalence of allergic diseases, and the not negligible costs, it is definitely needed that for any new diagnostic method the proof of efficacy is incontrovertible and evidence-based. Therefore the studies assessing the alternative methods should be randomized and controlled, and should report sensitivity, specificity and predictive values compared to reference methods. As a matter of fact, the majority of the clinical trials have a very low qualitative level, thus making the results often difficult to interpret.

In this article, the rationale and experimental evidence supporting the use of the various alternative diagnostic approaches will be reviewed.

LEUKOCYTOTOXIC TEST (BRYAN'S TEST)

RATIONALE

This test was firstly described in 1956, thus even before the discovery of IgE. It is based on the hypothesis that, in the presence of a noxious or not tolerated sub-

stance, leukocytes from the peripheral blood change their shape or even die and dissolve (11-12). The changes in leukocytes' shape are usually evaluated by optical microscopy, but new methods (using flow cytometers) have been introduced (ALCAT test).

EXPERIMENTAL EVIDENCE

A former study by Franklin and Lowell (13) documented the morphological changes of peripheral leukocytes, from ragweed-allergic subjects, when left in the presence of the allergen. Subsequently, Chambers and colleagues (14) failed to reproduce the phenomenon in polysensitized subjects, using the causal allergens for the tests. Liebermann (15) performed a controlled evaluation, and could demonstrate neither the presence of a cytotoxic effect of allergens, nor a significant correlation between the results of the test and the clinical picture. Moreover, the test displayed a wide variability within the same subject, that is a very low reproducibility. Another study (16) was carried out using a double blind controlled design. In this study, the high number of false positive and false negative results confirmed that the test has no diagnostic value. Similar results were obtained in other controlled studies performed by Lehman (17) and Stein (18). The automated method, using a flow cytometer provided inconclusive and controversial results as well (19-21). As a general consideration it is conceivable that the modifications of leukocytes somewhere observed, are provoked by physico-chemical factors (pH, temperature, osmolarity), rather than by a specific effect of the "noxious" substances (22-23).

At present the official position is that the leukocytotoxic test is of no value for the diagnosis of food allergy and, in fact, the United States, it is not refunded by the national healthcare system (24).

INTRADERMAL PROVOCATION/NEUTRALIZATION

RATIONALE

This procedure can be regarded as a diagnostic and therapeutic tool. It is based on the believe that intradermal administration of noxious or toxic substances provokes "untoward effects" within 10-12 minutes. The test is considered positive irrespective of the type of untoward effect observed or reported by the patient. Therefore, this test is clearly different from an allergen-specific provocation test.

In fact, the allergen specific challenge is carried out at the target organ level (nose, bronchi, conjunctiva) and

quantitatively assesses only few specific symptoms and parameters. Moreover, in the allergen-specific challenge, standardized extracts are used and a threshold dose is defined. On the contrary in the provocation/neutralization, the test substances are often not related to clinical history, all symptoms or signs are taken into account for defining a positive result, and no negative control is used (25). Thus, the test is not standardized and is largely dependant on the personal interpretation of the operator (26). After defining a positivity, the same substance that provoked the symptom(s) is given again in order to "neutralize" the adverse effect. In this second phase, the "neutralization" is performed with doses of the substance that can be either higher or lower than the provocative one, depending upon the operator. It has been claimed that the neutralization procedure can provoke the instant production of antibodies or the dissolution of immune complexes (25-27), but none of these hypothesis is supported by the present knowledge of the human immune system.

EXPERIMENTAL EVIDENCE

There are almost only descriptive reports in literature concerning the provocation/neutralization. Miller (28) described the favorable results obtained in a partially controlled study in 8 patients with food allergy. This study was flawed by the poor characterization of symptoms and the lack of a rigorous statistical evaluation. Another study was performed in double blind fashion by Crawford and colleagues (29): the test was performed in 61 patients with 5 common foods. The study failed to find any clinical correlation and the reproducibility was extremely unsatisfactory. Bronski assessed, in addition to symptoms, several objective parameters (leukocyte count, heart rate, peak expiratory flow rate) in 20 asthmatic children undergoing provocation/neutralization test and found no measurable change (30). Draper attempted to assess in 121 patients the correlation between the results of the intradermal test and the outcome of an oral challenge with the positive foods. The rate of false negative results was as high as 38%, therefore the Authors suggested to associate the provocation/neutralization and the *in vivo* food challenge (31). Again, in a double blind controlled study Kailin and Collier evaluated the beneficial effect of the neutralization after provocation, using saline as negative control. Active treatment were correctly identified in 70.6% of cases, but the negative control was judged as a positive treatment in 70% of cases, therefore the neutralization was no more effective than placebo (32). The provocation/neutralization is not devoid of side effects, and a near-fatal event was reported in a subject suffering from mastocytosis (33).

RATIONALE

The use of sublingual administration of allergens for diagnostic purposes was firstly suggested in 1944 by Hansel (34). The procedure is the same as for the intradermal method. Some drops of aqueous or glycerinated extract of the allergen (1/100 w/v) are given sublingually, and the patient is observed for 10 minutes. Any sign or symptom appearing within this time interval are considered as a positive result (35). Subsequently, when a positive reaction has been elicited, a neutralizing dose (highly diluted) of same substance is given in order to treat the symptoms. A possible variant is to measure the modification of the strength of contraction of skeletal muscles within 4 minutes after giving the suspected substances (so-called DRIA-test, by Associazione Ricerca Intolleranze Alimentari).

EXPERIMENTAL EVIDENCE

The efficacy of sublingual administration of food is described in anecdotic reports (34-37). All these reports are not controlled and not supported by scientific evaluations. On the other hand, the Food Allergy Committee of the American College of Allergists evaluated the use of the test during two consecutive years (1973-1974), and clearly demonstrated that the test cannot distinguish the active substances from the placebo (38-39). Kailin assessed in double blind fashion the efficiency of the test used by five different trained operators in subjects with ascertained food allergy. Also in this study, the test failed to distinguish between active and placebo substances (40). These data were recently replicated by Lehman (41). The available revisions of the literature (42-44) agree on the fact that the sublingual test is unreliable and of no diagnostic value. A recent document produced by the American College of Physicians (45) reviewed 91 studies. Only 15 were eligible for a careful analysis, and positive results were found in 8 studies. The document highlighted the poor methodological quality of the studies, the lack of adequate controls and randomization, and the absence of any standardization. Also the most recent study, published in 1988 (46), and providing favorable results is flawed by heavy methodological biases. Interestingly, it has been shown that when results are evaluated by independent physicians, unaware of the holistic implication of the methods, also the patients are unable to correctly identify active and placebo substances (47).

RATIONALE

This method is based on the assumption that a reduction of the muscular strength of contraction occurs when the subject comes into contact with a noxious or allergenic substance. Usually, the subject has to keep in hands or to touch (but the direct contact is not mandatory) a vial or a bottle containing the substance to test. The changes in muscle strength is evaluated directly by the examiner (48, 49). With children the assessment is carried out in the parent. It has been claimed that allergic mechanisms can inhibit the neuromuscular coupling (50, 51), despite there is no scientific demonstration that such an effect exists (52) and some obscure concepts as "hepatic distress" or "energy fields" are often mentioned. It is hard to believe from a scientific viewpoint that the absence of a direct contact with the culprit substance can provoke any change in the body's physiology. Nevertheless, the procedure is not invasive and obviously safe, therefore it has gained a great popularity.

EXPERIMENTAL EVIDENCE

There is a single controlled double blind study evaluating the effectiveness of the kinesiologic test (53). This study failed to demonstrate any diagnostic correlation and reproducibility of the procedure. In another trial (54), the possible correlation between the kinesiologic test and some immunological parameters (specific IgE, IgG, immune complexes) was studied. The Authors claimed that a positive correlation was found in 19/21 of the tested allergens. Nevertheless, the best correlation was found for IgGs, that have a negligible pathogenic significance in food allergy (55).

CARDIO-AURICULAR REFLEX AND PULSE TEST

This test is based on the traditional acupuncture, where a reflex linking the ear and the heart is described. Thus, it is claimed that putting the offending substance in proximity of the ear can modify the heart rate (56). There are several variants involving different ways of administration of the suspected allergen (intradermal, oral, inhaled), and a change (increase or decrease) of at least 10 beats/min in the pulse rate is considered a positive response.

There is no scientific rationale, and no experimental or quasi-experimental study on the value of this test, that is still largely popular, has been ever performed.

ELECTRODERMAL TESTS (ELECTROACUPUNCTURE ACCORDING TO VOLL)

RATIONALE

It is hypothesised that the patient's response towards an offending or not tolerated substance can be identified by measuring the changes in cutaneous conduction at specific points, usually the same of Chinese acupuncture points (57, 58). Thus, altered skin electropotentials at acupuncture points or along meridians may indicate an electromagnetic perturbation transferred by "incompatible" substances (even in closed vials). This approach is sometimes regarded by "functionalistic medicine" as an ideal link between acupuncture, homeopathy and traditional medicine (59, 60).

A variety of electrodermal machines (Dermatron, DRIA test Vega Devices, segment electrography) are now available and commercialized, but they all share the same general principles. Briefly, the devices measure the skin conductivity at acupuncture points. The operator delivers a direct current of few mA (low voltage), for about 1 second by applying an electrode at the chosen skin points. The body impedance between the skin point and another electrode is then measured. The test substance are inserted, contained in closed vials, in the electrical circuit. The test is appealing, because it is non invasive, and because of the use of an electronic apparatus that gives a scientific appearance to the procedure.

EXPERIMENTAL EVIDENCE

Several studies using the electrodermal tests for diagnosing allergies have been published, and almost all agreed that the diagnostic value, if any, is negligible (61-64). One single study have provided favourable results (65). There are two recent well-conducted trials, using the randomized, double blind, placebo controlled method. The study by Lewith (64) involved 15 subjects sensitized to cat or mite and 15 nonatopic controls. The evaluations were performed double blindly in triplicate by three different operators. The test was unable to distinguish between atopic and nonatopic subjects and to detect correctly the sensitizations. Another study was carried out with similar methodology in 80 atopic and 30 nonatopic subjects (62) and lead to similar results. The electrodermal test could not identify the allergic subjects and, in addition, displayed an unacceptable variability. Despite these experimental results, it is noteworthy that some public healthcare systems still refund for the electrodermal tests (66).

BIORESONANCE

This approach is based on the believing that human bodies emits a wide spectrum of electromagnetic waves, with positive or negative properties. Bioresonance devices are thought to "filter" those waves, cutting off those undesired (67-68), therefore they can be used for both diagnosis and therapy. No scientific demonstration of bioelectrical waves and of the possibility of filtering them has ever been provided under controlled conditions. There are two controlled double blind studies, one in adult patients with allergic rhinitis (69), and one in children with atopic eczema (70). Both studies failed to demonstrate any diagnostic or therapeutic value of the bioresonance method.

HAIR ANALYSIS

RATIONALE

The hair analysis is currently employed in forensic pathology to detect the presence of heavy metals or other substances (71). Starting from this basis, it has been claimed that the measurement of heavy metals (or the depletion of oligoelements) can be used to diagnose and treat allergies and intolerances (72). For instance, an excess of heavy metals has been hypothetically associated with the hyperkinetic syndrome in children. Nevertheless, there is no demonstration that heavy metals or other substances in the hair can affect the development or pathogenesis of allergic diseases. Other uses of the hair analysis pertain much more to the magical sphere than to scientific methods.

EXPERIMENTAL EVIDENCE

There is a single controlled double blind study, performed in fish-allergic patients (73). Determinations were carried out in 5 independent laboratories. All operators were unable to correctly detect the allergic individuals or the causal allergen. Moreover the reproducibility of the assay was inferior to 10% (73). Another evaluation analysis performed in the USA in 13 different commercial laboratories, confirmed that the hair analysis is of no value in allergy diagnosis (74).

IGG AS A DIAGNOSTIC TOOL

The involvement of specific IgG in the pathogenesis of adverse reaction to foods (in particular in paucisymptomatic or chronic diseases) can be hypothesized. The causal role of IgG ha, in fact, been suggested for: irri-

table bowel, migraine, chronic fatigue syndromes and similar diseases. Nevertheless, the real role of IgG has not yet been confirmed. IgE-mediated diseases are characterized by a strict exposure-effect relationship and by the reproducibility of the clinical symptoms. These aspects are partly dependent by the fact that in the atopic subject the production of specific IgE is ongoing and continuous. This is not the case of an IgG-mediated response, where the production of high levels of IgG (sufficient for instance to form immune complexes) requires a continuous and prolonged exposure. Therefore, the diagnosis of an IgG-related food reaction is difficult in principle, since the strict cause-effect relationship lacks. The diagnosis of IgG-mediated forms relies on the detection of the allergen-specific immunoglobulins, through ELISA methods, with allergen-coated plates. At present, this kind of test has several accuracy and efficiency limitations, mainly due to technical factors.

SCIENTIFIC EVIDENCE

In some studies both in humans and animals, the presence of circulating food-specific IgGs has been previously demonstrated (75-78). Nevertheless, a demonstration of the clinical role of these IgG (i.e. the causal role in diseases) still lacks.

DISCUSSION

The review of the available literature concerning the use of complementary/alternative diagnostic tests, suggests some considerations:

- the use of these methods is widespread and, probably, increasing. They are appealing to patients because of a good safety profile, and the usual absence of a direct contact with the allergen/noxious substances. Moreover, these tests are part of holistic medicines, where the physician-to-patient relationship is close and relevant.
- Most of the commercialized and currently used methods are not recent, and they have been repeatedly tested in the past, with negative or controversial results.
- Many trials have been performed and designed by non-specialized health operators, this resulting in a poor methodological quality of the study, in inadequate controls/analysis and in an incorrect selection of patients
- The vast majority of these tests are used for the diagnosis of food allergy/food intolerance. In this field, the diagnosis is often difficult, the definition of the diseases themselves is usually vague, and heterogeneous clinical manifestations can be attributed to an "allergic" mechanism.

The lack of a scientific basis for the majority of these tests and the poor diagnostic performances have both socio-economic and clinical consequences. The misuse and abuse of alternative diagnostic tests, especially in paediatric age can result in unjustified dietary restrictions with malnutrition or growth problems (79), even to life-threatening events (80). In adults, the negative consequences of misdiagnosis are usually less dramatic; nevertheless the negative impact on the quality of life caused by unjustified dietary restrictions must be taken into account. Moreover there is also the real risk of diagnostic errors, and of the misdiagnosis of other concurrent disorders (81-85).

Of course, one of the most important reasons of the success of the alternative tests (together with is the simple execution and the non invasivity) is the close relationship between the patient and the operator, that is common to all holistic forms of medicine.

Those patients using or willing to use alternative diagnostics should be informed in detail of the experimental evidences supporting them (86, 87) and should be warned against the risks of misdiagnosis. Thus, the correct education/information of the patient is essential and mandatory.

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SPECIAL MEDICAL SOCIETIES OFFER EVIDENCE-BASED CONCLUSIONS ON INHALED STEROID TREATMENT FOR ASTHMA, AAAAI, AND ACAAI CONCLUDE BENEFITS OF ICS TREATMENT OUTWEIGH RISKS

(NORTHBROOK, IL, December 9, 2003) - Inhaled corticosteroid (ICS) therapy remains the gold standard of asthma treatment, according to findings from a systematic evidence review released today by the American College of Chest Physicians (ACCP), the American Academy of Allergy, Asthma, and Immunology (AAAAI), and the American College of Allergy, Asthma, and Immunology (ACAAI). Published in the December issue of CHEST, the peer-reviewed journal of the ACCP, the review offers evidence-based conclusions on several prominent risks associated with ICS therapy for the treatment of adult and pediatric asthma.

"ICS therapy has been the gold standard in asthma treatment for 20 years because of its proven effectiveness. However, since the inception of ICS therapy, physicians have been concerned about side effects particularly in special populations, such as children, women, and the elderly," said lead author Frank T. Leone, MD, MS, FCCP, Thomas Jefferson University, Philadelphia, PA. "After a systematic and accurate review of the proven risks, we can say with confidence that the majority of evidence supports the conclusion that the clinical effectiveness of ICS therapy decidedly outweighs the proven risks."

An expert panel with representatives from the ACCP, the AAAAI, and the ACAAI identified critical questions that impact decisions regarding the use of ICS therapy in relation to the five adult and pediatric risk areas of bone mineral density (BMD), cataracts, glaucoma, growth retardation, and skin thinning. Panel members reviewed 108 asthma studies related to ICS therapy complications and summarized all relevant evidence for each risk area. A consensus statement was provided for each risk area along with a grade to reflect the quantity and quality of evidence supporting each conclusion.

Overall, the panel concluded that the benefits associated with ICS use greatly exceed the risks. In regards to the effect of ICS therapy on BMD, the panel strongly supported the conclusion that ICS use is not associated with a reduction in BMD in chil-

dren with asthma. The panel also supported the conclusion that ICS use is associated with skin thinning and easy bruising in adults and children, but that dose, duration of use, and patient gender are important variables affecting overall risk. In addition, the panel fully supported the conclusion that ICS therapy is associated with a decrease in short-term growth rates in children, but that the overall effect is small and may not be sustained with long-term therapy.

According to the panel, conclusions regarding the effect of ICS therapy on BMD in adults and the effect of ICS therapy on the development of cataracts and glaucoma were insubstantial because they were only supported by conflicting or insufficient data.

"With more than 15 million people in the United States living with asthma, adverse events related to asthma therapy can greatly impact public health," said Richard S. Irwin, MD, FCCP, President of the American College of Chest Physicians. "The joint effort between the ACCP, AAAAI, and ACAAI to provide physicians with conclusions on the risks of ICS use signifies the continuous support of evidence-based medicine by these medical societies and their commitment to patient-focused care."

CHEST is a peer-reviewed journal published by the ACCP. It is available online each month at www.chestjournal.org. ACCP represents more than 15,700 members who provide clinical, respiratory, and cardiothoracic patient care in the United States and throughout the world. ACCP's mission is to promote the prevention and treatment of diseases of the chest through leadership, education, research, and communication.

The American College of Allergy, Asthma and Immunology (ACAAI) is a professional medical organization, headquartered in Arlington Heights, Illinois, comprising 4,963 qualified allergists-immunologists and related health-care professionals. The ACAAI is dedicated to the clinical practice of allergy, asthma and immunology through education and research to promote the highest quality of patient care.