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SECOND MAIN SUBJECT: DEBATE ON THE USE OF SPECIFIC *IN VITRO* DIAGNOSTIC METHODS IN PRIMARY HEALTH CARE

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Debate on the use of specific *in vitro* diagnostic methods in Primary Health Care

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INTRODUCTION AND USEFULNESS IN PAEDIATRICS

The observation of a clear increase in the incidence of allergic disorders is an evident fact in our professional routine practice. This fact implies, for those physicians who care exclusively for patients from the public health system, that we must carry out a number of measures aimed at chronological reshuffling of the population in the waiting list. In

other words, we have to try to give priority to those clinical disorders that will most rapidly benefit from our studies in terms of prevention, elimination of the causative allergen or specific therapy.

Which are the measures a hospital paediatric allergologist can put in motion for an optimal management of his waiting list?

In the first place, and this should be considered his obligation, he should request more resources from the adequate instances, in the form of more specialised health care personnel that will be able to attend, with the least permissible delay, those patients sent to us with a "preferent" label from the basic health care areas.

The allergologist will then have to hear a volume of mostly negative explanations from the local authorities. These explanations will be based in economicist terms and will usually ignore a fundamental general principle of our Constitution, that of equity, which should mean that every Spaniard has the right to be treated under equal conditions. Having heard all this, the allergologist will have to put his imagination seriously at work in order to devise ways and means to benefit those disorders, those patients who most need it, within that hypothetical equality.

The first step in this endeavour will be, after the obvious and oftentimes useless personal efforts to find imaginative ways to get more human resources through research grants, collaboration scholarships, clinical studies, etc., to try to assess and classify the interconsultation request slips from the primary health care centres in a completely subjective way. And this must be subjective and based in the experience garnered over long years of work. This experience will detect those "preferent" interconsultations requested because of extraclinical reasons, those mistaken requests due to lack of knowledge, those unforgivable delays in submitting the patient for specialised care, and finally those slips that should not have been completed. Let me now consider one by one those incidences, in the light of our own clinical practice.

— An interconsultation request slip (or "CH", for *consulta hospitalaria*, as they are called in Catalonia) with a "preferent" annotation does not always necessarily mean that that consultation should be moved forward in time. We all know that the pressure from the parents, caused by a problem the severity of which is inversely proportional to their stress, may sometimes cause the paediatrician to request "preferent" attention.

– Our speciality is sometimes, and most particularly so in the case of the adult population, a sort of mixed bag into which problems are consigned that are far removed from a suspected allergic condition. Quite often conditions not related to hypersensitivity phenomena have not been adequately ruled out, possibly because of the requesting primary physician's lack of knowledge. A further contribution to this problem is the fact that expressions such as "this must be an allergy", or "whoever is not allergic to something?" have become embedded into the minds of a large proportion of the patients and often favour or even force the submission of the patient to the specialist.

– At the other end of the spectrum, there are often interconsultation requests that arrive at our Clinics with an excessive delay, caused by an exaggerated zeal in retaining the patient and not requesting interconsultation until the disease has become clearly chronified.

– We still receive, although a decreasing trend can be perceived, interconsultation request slips that have not been adequately completed, and that bear a simple "RV" annotation ("request visit") as the only sign of life of the primary health care physician. The most immediate reaction is to return the slip, but it is also logical to remember that each of those request slips represents one patient and that the patient is himself not at fault. The usual result is that the request is accepted without the slightest idea about the need for specialised attention or its degree of priority.

Thus, this way of assigning priorities on the basis of the simple lecture of the request slip is completely subjective, and is therefore prone to wrongness.

The best answer to the problem would be that of a true co-ordination between us specialists and our main "providers", the Primary Health Care GP's in the basic health care areas and the paediatricians in our catchment areas, and of trying to find objective atopy screening elements that have been scientifically tested and that will turn the correct priority assignation of the assistential demand into reality.

A suggestive clinical history already constitutes sufficient grounds for sending a patient to the allergologist, but the excessive assistential demand and the scarcity of specialised personnel available give rise to large waiting lists. This problem still awaits solution.

It was common everyday practice until some years ago, and it is still so in some not-updated areas, to label as "allergy" the presence of high levels of serum IgE. This analysis is rather easy to perform at the laboratories of the Health Care Centres. However, the "high

IgE = allergy" axiom does not give due consideration to the sensitivity and specificity of the test, to the spectrum of non-allergic possibilities in children with elevated IgE, or to the possible association of normal serum IgE levels to truly allergic disorders.

In the light of these considerations we first asked us how we might give orientation to our providers (in my particular case, the Area and Primary Health Care Paediatricians) in the use of *in vitro* tests for a better screening of the disorders they send to us. At the same time, we tried to establish a critical assessment of the *pros* and *cons* of such a way of acting.

In an initial phase we held meetings with the paediatricians in our area to explain to them the technical aspects of a –for them– novel analytical procedure that, correctly assessed in the context of a suggestive clinical history, might facilitate an earlier referral to the specialist.

WHAT IS "PHADIATOP"?

Although the name will be new to many, Phadiatop was first presented at the scientific level in 1987, in a paper in *Clinical Allergy* with the title "Phadiatop, a new screening test for IgE antibodies".

This new test is based on the same principles as the RAST, and it was originally created for detecting allergy to pneumoallergens with a single test. A so-called "paediatric" kit then appeared, combining the pneumoallergens with the most allergenic foodstuffs encountered in the early phases of life.

The original idea was conceived, as stated in the original paper, with the aim of providing, after an analysis of the growing problem of the incidence of allergic conditions, a simple tool that would be available to allergologists and to other clinicians and that would help reduce the volume of prior consultations through a recognition and diagnosis of allergy.

The first Phadiatop was tested in Great Britain, and it replaced the trend to request RAST to *Dermaphagoides pteronyssinus*, grass pollens and cat dander as a screening for allergy. The undisclosed formulation included a variety of pollens, moulds and animal epithelia. The results of that test clearly favoured the used of Phadiatop.

A large number of works and papers have –in a technical sense– passed the examination and have provided optimal figures about the sensitivity and specificity of this *in vitro* test. The still-smouldering debate by the more renitent groups has turned to

other non-scientific aspects, as we shall discuss later.

Recently, in 1997, the National Institutes of Health Guidelines on Asthma included the *in vitro* tests for allergen identification as a proper tool and help in the management of asthma, the main chronic disease in childhood and the number one cause of hospital admission and absenteeism.

At this point, and without the least demerit to the main diagnostic help we allergologists have available to us, the skin tests, we should review the possible handicaps encountered in their use and assessment.

The results of the skin tests may be altered depending on the number of mast cells present, on the activity of those mast cells, on the binding of IgE to those cells, and on a number of factors linked to mast cell reactivity, such as sensorineural activity, hormone influence on receptors, tissue remodelling or muscle spasms. Further factors to remember are skin diseases and the well-known drug therapies that might modify the skin test results.

Further to these factors, we should also remember other variables that may influence the results of skin tests, such as the following:

False negative results:

- Inappropriate storage of the allergens.
- Inappropriate administration.
- Factors inherent to the patient, such as age, skin region, time of day, skin temperature.
- Refractory period.
- Drug-caused inhibition.
- Subjective interpretation.

False positive results:

- Inappropriate preparation and administration of the allergen.
- Remaining past sensitivity.
- Disparity to the clinical sensitivity.
- Subjective interpretation.

For these reasons, and in the case here concerned of detection of the atopic individuals in Primary Health Care, the recommended *gold standard* has been the use of the clinical judgement in combining the clinical history with the interpretation of an *in vitro* screening tailored with the locally most significant allergens.

We shall now discuss some of the many published papers which merit commentary because of some relevant and salient fact.

In our own occupational environment there has been for a long time a widespread rejection of the idea of putting *in vitro* screening procedures in the hands of the Primary Health Care professionals. The grounds for that rejection may be classed as both clear and dark: clear in expressing disconformity with the possibility of equalling a negative Phadiatop to a negative allergologic study, and dark in trying to avoid the possible trend towards retaining the patient in Primary Health Care and not referring him or her to a specialist for aetiological diagnosis.

There were no doubts based on technical reasons or on feasibility, but only those concerned with the possibility that this diagnostic tool, this direct heterologous enzymeimmunoassay that expresses its results as "positive" or "negative", might constitute a barrier in the logical evolution of the patient towards the allergologist. The answer, from our point of view, is quite simple: use your common sense. If, in spite of a negative test result, there is still a suspicion of atopy, refer the child to the allergologist. We cannot expect, in Medicine, tests that have 100% effectiveness, and we should know how to explain this to the Primary Health Care Paediatricians in our area of influence.

Ibero *et al.*, in 1993, designed one of the earliest studies for assessing the clinical yield of a simple analytical technique, "Phadiatop Pediátrico" (paediatric Phadiatop), as a method for atopy screening.

They studied 92 consecutive patients with a mean age of 7.3 years, who had been referred for the first time to an Allergy Unit because of bronchial asthma, rhinitis, spasmodic cough or urticaria. In all these cases the study comprised a detailed clinical anamnesis, prick tests with 16 common allergens (and with alimentary allergens when the clinical history suggested it), total IgE quantitation, and the paediatric Phadiatop.

Their conclusions were that, if the skin tests are accepted as the most discriminative test in the assessment of atopic sensitization, the total IgE had 68% sensitivity, 78% specificity, an 83% positive predictive value and a 61% negative predictive value, while the corresponding results for the paediatric Phadiatop were 88% sensitivity, 92% specificity, 94% positive predictive value and 83% negative predictive value. For these reasons, they state that the paediatric Phadiatop is a reliable technique in the overall screening of allergy because of its high sensitivity and specificity.

The group of Johansson, in Sweden, published in 1995 (in *Allergy*) a comparative study of the diagnostic properties of the paediatric Phadiatop and the standard Phadiatop in a population of 193 children with a family history of atopy. As compared to the standard Phadiatop, the paediatric one contains less inhalant allergens and associates a mixture of the foodstuffs most often causing food allergy. Always with the reference criterion of positive skin tests to at least one allergen, in the case of Phadiatop they observed 86% sensitivity, 94% specificity and 92% effectiveness, with lower values for the paediatric Phadiatop.

They also observed a 9% discrepancy between the results of the standard and the paediatric Phadiatop, which may be attributed to the fact that the paediatric version is unable to detect children with tree pollen allergy. They therefore recommended that the standard version be used from the age of 5 – 6 years onwards, adding RAST to a food mixture as an atopy screening, at least in those areas where birch pollen is a frequent allergen.

In our own environment we can obviate that problem by using the standard inhalant Phadiatop together with Phadiatop Fx5, a mixture of the foodstuffs most frequently causing allergy in particular in the paediatric population.

A more specialised study carried out by the ENT Department of the University of Munich (Germany) has assessed the diagnostic efficacy of Phadiatop in allergic rhinitis, with the novelty of studying this technique in the nasal secretion fluid besides the classical application in serum. This study encompassed 267 adult patients with a diagnosis of allergic rhinitis established through the conventional methods (clinical history, skin tests, and determination of reagine antibodies and nasal challenge tests).

Their results show for Phadiatop a sensitivity of 98.1% and 79%, when applied respectively to the serum or to the nasal secretion. The specificity was 95.9% in serum and 97.5% in nasal secretions. These investigators concluded that the Phadiatop assay on nasal secretion fluid represents an important additional method leading to increased specificity of the determination.

CONCLUDING CONSIDERATIONS

In an environment guided by economic considerations (with the health care environment foremost in this trend), it is important to know the role the Local

Administrations play in the acquisition of "new and novel products". Specifically in our Health Care Area, it is quite difficult to introduce novel techniques and procedures that are not already contained in the Services Catalogue. Any small doubt that the Administration collects from any physician group, or even from isolated physicians, will be magnified, and the negative answer is immediate.

Faced with this problem, those physicians like us who believe that techniques such as Phadiatop are interesting in the management of the large groups of patients seen in Primary Health Care and who should be studied by the adequate specialists are forced to devise imaginative –and unpublishable– ways and means that will, in the end, lead to the desired results.

The actual cost of a Phadiatop determination is similar to that of a specific IgE quantitation, and we have all seen expensive analytical procedures (such as for instance the Multi-RAST), the results of which are not correctly interpreted by the requesting physician.

The delay in referring an allergic patient to the specialist entails an increase in the direct costs (drugs) and also in the indirect costs (school and work absenteeism). A typical example would be that of the allergic patient with cat dander hypersensitivity. Until he is seen by the specialist, this patient –and his asthma with him– will run the gauntlet of a variety of consultations without having had an aetiological diagnosis established. Phadiatop, with its high degree of efficacy, might have detected this aetiology and led to a prompt intervention by the allergologist.

We have stated at the beginning that it is important to know how to explain to the Area Paediatricians the advantages and also the limitations of this technique, so that they may always use their reason on any analysis result. Thus, and particularly in the case of negative Phadiatop results, they must know and consider that there are sensitizations to certain foodstuffs, to occupational allergens (particularly in adults), to insect stings or to exotic animals, such as birds or hamsters, that cannot be detected by this technique. However, if the patients are also sensitized to inhalant allergens that are common in our environment, the Phadiatop result will be positive regardless of the previous argument.

Pharmacia & Upjohn has been criticised because of maintaining the actual composition of Phadiatop secret for commercial reasons. A more important reason for restricting this information appears to exist, however, and that reason is avoiding and preventing the overuse of this test in the sense of prescribing hyposensitizing

therapy with the same extract composition as in the known diagnostic mixture. The manufacturers consider that restricting the information about the composition is the best way to combat overuse or abuse without detracting from the clinical value of the test.

To conclude I wish to state that, after two years of experience and co-operation with the Primary Health Care paediatricians, my final conclusion is that with the earlier assessment of the patient as atopic or non-atopic, together with our own ability to assign priorities on the basis of that information and achieve high levels of positivity in our allergological studies, the final link in the chain, the patient himself, will be the one to benefit from being correctly treated by the adequate specialist.

Need for aetiological allergy diagnosis in Primary Health Care

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There is already a special sensibility on the side of the health care managers regarding the advisability of an aetiological diagnosis of allergy in Primary Health Care. A good demonstration of that sensibility is the rather recent introduction of the "Referral Guidelines in Allergic Disorders: An Actuation Consensus between Primary and Specialised Health Care" (*Pautas de derivación en las enfermedades alérgicas, consenso de actuación entre Atención Primaria y Atención Especializada*)². This document was prepared upon the request of the General Directorate for Primary and Specialised Health Care of the Spanish National Institute of Health, and the protocol was signed by the parties on September 1st, 1997. The participants in its elaboration were Dr. Enrique Buendía as President of the Spanish Society of Allergology and Clinical Immunology, Dr. Albert Planes as President of the Spanish Society of Family and Community Medicine, Dr. Juan Rodríguez as President of the Spanish Society of Rural and General Medicine, and Dr. José del Pozo as President of the Spanish Society of Extrahospitalary Paediatrics.

In its introduction, this document reviews and discusses the increasing incidence and prevalence of this type of diseases, and the need for an aetiological diag-

nosis in order to implement preventive measures and/or specific therapies that might have an expression in the patients' quality of life.

We shall now review, among the guidelines proposed in this document, those related to respiratory conditions.

In the case of rhinitis, the document concisely reviews its definition and evolution and the value of the nasal cytology analyses, and established an algorithm for the referral to an Allergy Unit of patients with suspected seasonal or perennial allergic rhinitis.

Regarding bronchial asthma, the Guidelines state that the following patients should be referred for specialised allergological study:

- Patients with occupational asthma.
- Patients with a founded suspicion of allergic disease, for aetiological diagnosis and assessment of the therapeutic possibilities.
- Patients with persistent severe asthma.
- Other patients, whenever the Primary Health Care physician considers such referral appropriate and necessary because of the existence of controversial diagnoses or when there are problems in establishing a concrete diagnosis.

Thus, Allergology is established as the referral speciality for all cases with suspected allergic aetiology, or when there are problems in achieving control of the symptomatology.

However, the Guidelines do not establish any objective measure as sufficiently sensitive for discriminating between atopic and non-atopic conditions, particularly in doubtful cases.

Generally speaking, the Primary Health Care physician may approach this problem in three different ways: the traditional one of quantifying the total serum IgE levels, that of requesting a panel of specific serum IgE determinations, or that of requesting tests to a panel of allergens.

The quantification of the total serum IgE levels has become traditionally established as one of the guiding parameters in the diagnosis of suspected atopic conditions. It has been demonstrated that the total serum IgE levels tend to be higher in allergic children and adults when compared to the non-allergic population. However, the diagnostic value of this parameter is limited³.

In the adult population, elevated total IgE levels are found in 62% of all patients with extrinsic rhinitis and in 76% of all patients with allergic asthma, but also in 10% of all patients with non-allergic rhinitis and in 20% of all intrinsic asthmatics⁴. In a study by Wittig,