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The prick by prick test is safe and reliable in 58 children with atopic dermatitis and food allergy

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Abstract. – The initial diagnostic approach of food allergy (FA) is to take a detailed history and to perform a careful physical examination in the gastrointestinal, cutaneous and respiratory systems. Subsequently, verification of the relationship between the symptom(s) and the ingestion of the offending food(s) is mandatory, and finally determination of the immunologic mechanisms involved with in vivo and in vitro tests should be performed. The diagnosis of FA in infancy and in childhood is a challenge both for the pediatrician and allergist because it can be easily accomplished only when there is a correlation between the ingestion of the offending food(s) and the onset of the symptoms, and when it can be demonstrated that these symptoms are the consequence of an immunological reaction. However the underlying immunologic mechanisms may be difficult to document, and the only immunologic mechanism easily to prove in current practice is the IgE-mediated one. In this paper on 58 food-allergic children and 60 nonatopic controls we demonstrate that the prick + prick (P+P) tests are very effective and easy to perform. In addition we stress that FA cannot be excluded only because skin prick tests (SPTs) are negative, as recently suggested.

Key Words:

Atopy, Children, Diagnosis, Skin prick tests, Prick + prick tests, Oral food challenge.

Introduction

The cumulated prevalence of allergic diseases, especially atopic dermatitis (AD) and FA has now reached figures as high as 23-34% during the very first years of life[1-3]. It is therefore worthwhile to early diagnose atopy with reliable and feasible methods[3] to stop the atopic march[2]. Studies have reported that some fruits and vegetables can be denaturated during the processing procedure of commercial extracts, thus losing their natural allergenicity[4].

Since several years the P+P technique for fresh fruits and vegetables has been shown to be a more reliable method than the commercial extracts, and in addition to being easily arranged, it could be a safe and useful diagnostic method[5]. In contrast, SPTs can be unreliable[5], in addition to provoking untoward reactions, since the appearance of serious clinical reactions has been recorded after the application to the skin of minimal quantities of cow's milk (CM)[6].

The technique is very simple. One pricks a normal lancet into the fruit or vegetables, and immediately thereafter into the skin[5,7,8]. Otherwise[8] the skin can be pricked first, and a piece of fruit/vegetable is firmly taped to this place, or rubbed on this place, or viceversa: the skin is rubbed first and pricked immediately thereafter.

An original technique was further devised by Oranje[9] called SAFT (Skin application food test), consisting in the application of fresh food, that is in the same state as it was consumed, on the back of children using large Finn chambers and read after regular intervals[10]. However this technique without pricking appears to be a variety of the patch test.

As yet, several studies employed P+P for a wide range of foods, including fruits and vegetables (Table I)[4,7,8,10-20]. We have previously P+P tested 128 children with AD, but only 14,6% of children had positive oral food challenges (OFCs) (Table II)[18]. Recently this technique was proposed to ascertain whether hydrolysate formulas (HF) can safely be given to children with CM allergy (CMA)[20], and was also adapted to diagnose latex allergy[21].

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Table I. Studies done with the P+P method.

Authors (Ref)	Year	Fresh foods tested
Hannuksela and Lahti[7]	1978	Apple, carrot, potato
Andersen et al[17]	1978	Apple, potato
Dreborg and Foucard[8]	1983	Apple, carrot, potato
Pastorello[14]	1985	Apple, peach, plum, pear, cherry, apricot, banana
Ispano et al[15]	1985	Apple, onion, tomato
Sacerdoti et al[13]	1987	Wheat, egg, CM, chocolate, fish, tomato, etc
D'Urso[16]	1987	CM, egg, fish
De Martino et al[11]	1988	Apple, peach, tomato, pear, egg, CM
Ortolani et al[12]	1988-89	Apple, peach, apricot,
Cantani e Mastrantoni[18]	1990	Banana, apple, carrot, potato, tomato, wheat, egg,
Sampson et al[20]	1991	Hydrolysate formula
Ragno et al[19]	1993	3 hydrolysate formulas
deWaard-van der Spek[10]	1998	CM, egg, peanut

This prospective study was undertaken to evaluate P+P in comparison with SPTs in the diagnosis of AD due to FA, and to assess P+P effectiveness and reliability. We adapted the technique for CM, egg, and wheat, the most common foods of the children diet and frequently suggested to induce FA even by the first year of life[2].

Patients and Methods

Among the children consecutively attending our Division we selected 58 children aged 9 months-12 years with multiple sensitizations to foods previously diagnosed with SPTs, RAST, and elimination diets. Sixty matched for sex and age, nonatopic children recruited during the same period from our outpatient clinic formed the control group.

The children were subjected to the diagnostic protocol of the Division, including SPTs, P+Ps for CM, egg, and wheat, and OFCs. For P+P tests we employed fresh, uncooked foods bought locally, CM and emulsified whole raw egg, while for wheat we prepared a mixture of flour and boiled water (2:1-1.25).

Skin Prick Tests

Appropriate emergency equipment and medications were available on site. Antihistamine drugs and topical steroids were stopped at least 2 weeks before the application of the SPTs. Skin testing was done at baseline by the prick method on the volar surface of the forearm by a trained in allergy doctor with

Table II. Results in previously P+P tested 128 children with atopic dermatitis.

Food	Positive P + Ps No. of children (%)		Positive oral food challenges No. of children (%)	
Orange	13	10	8	6
Peanut	9	7	1	0.8
Banana	58	45	1	0.8
Carrot	13	10	0	0
Chocolate	7	5	0	0
Strawberry	13	10	0	0
Apple	40	31	1	0.8
Potato	41	32	5	4
Tomato	121	95	30	23

In these previously P + P tested 128 children with AD only 14.6% of children had positive OFCs. From reference[18].

the co-operation of a qualified nurse. The skin was marked with a ballpoint pen for the allergens to be tested. The babies were then tested with: histamine hydrochloride (1 mg/ml) as a positive control and isotonic saline as a negative control. We continued with a battery of food and inhalant allergens, including whole CM protein, casein, lactalbumin, egg, wheat, fish, soy, *Dermatophagoides pteronyssinus*, *Alternaria alternata*, *Lolium perenne*, *Olea europea* and *Parietaria officinalis* (SARM, Roma, Italy). The diagnostic extract of each individual allergen was placed on the volar surface of the forearm as drops through which the skin was superficially pricked with a straight pin for one second. A new pin was used for each P+P/SPT and then discarded, and the drop of the extract was then wiped off about one minute after the prick[22].

P+P/SPTs were read at 20 minutes and considered positive as follows:

+ when the wheal was the half of the histamine wheal;
++ when the wheal was equal to the histamine wheal;
+++ when the wheal was two-fold the histamine wheal;
++++ when the wheal was more than two-fold the histamine wheal[22].

We took for positive only children with a +++ or ++++ reaction, that is a wheal ≥ 3 mm with an area = 7 mm^2 (cut-off) We considered as positive only the children with a mean wheal diameter of 3 mm or larger than the negative (saline) control. A positive (histamine) control was performed to ensure the absence of any antihistamine drug interference[23].

Challenge Test

At the end of the normal 4-6 wk period, to confirm the P+P results, 58 OFCs for CM, egg, and wheat were performed in the hospital under observation in a unit staffed to undertake emergency equipment. In the study children CM, egg and wheat were administered as follows: a drop of CM (or of emulsified raw egg, or wheat as previously detailed) was put upon the inner border of the lower lip. If no reaction ensued, a further 5 ml of CM (or 1 ml of emulsioned raw egg, or 5 g of bread) were given after 5 minutes, and after 30 minutes 100 ml of CM or half-boiled egg, or 100 g of bread. The reactions were defined as immediate if the first symptoms occurred within two hours of ingesting the food antigen, and delayed if the first symptoms occurred within four hours. If any symptoms secondary to the OFCs were observed, the OFC in the hospital was terminated. After the last administration of the tested food the children were watched for at least 4 hours and then discharged[24].

The same procedure was done in the control children.

Informed Consent

Informed consent was obtained from parents of each child. The study was approved from the "Committee for ethics" of our institution.

Statistical Analysis

Data were statistically analyzed using the Student t and the X2 tests.

Results

The P+P method was 14 times positive for CM, 30 for egg and 12 for wheat. There were 18 positive SPTs for CM, 30 for egg, and 16 for wheat. (p = 0.0093). A concordance between the two techniques was operative for CM in 14/18 cases (77.8%), for egg in 30/30 cases (100%) and for wheat in 12/16 cases (75%). The sensitivity, specificity and predictive positive value (PPV)[25] of P+Ps were 100% for CM, for egg specificity and PPV, and for wheat only sensitivity (Table III).

In the control children, as regards SPTs there were 5 positive for CM, 6 for egg, and 4 for wheat (p = 0.0291), and for P+Ps 5 positive for CM, 8 for egg and 2 for wheat (p = 0.0015).

In the OFCs, 17/18 study children with positive SPTs for CM tested positive for CM, 29/30 with positive SPTs for egg tested positive for egg, and 16/18 with positive SPTs for wheat tested positive for wheat (Table IV) (p = 0.0202). Only one control child had an OFC positive for CM. No untoward reactions were noted.

Table III. Criteria of analytical reliability: comparison between SPTs and P+Ps (%).

	SPTs			P + Ps		
	CM	*Egg*	*Wheat*	*CM*	*Egg*	*Wheat*
Sensitivity	56.3	51.7	27.6	24.1	51.7	20
Specificity	91.6	90	93.3	91.6	77.1	96.6
Predictive value +	78.3	83.3	80	73.6	83.3	85.7
Predictive value -	57.9	65.8	57.1	55.5	65.8	54.7
Effectiveness	49.1	45.7	61	58.4	71.1	59.3

Discussion

This study shows that OFCs confirmed 62/64 (96.8%) SPT diagnoses while P+P diagnoses were positive in 56/62 OFC cases (90.3%) (NS). Usually, both diagnosis and treatment are difficult to assess, since the much in vogue diagnostic items are SPTs and RAST, that yield varying results in term of sensitivity, specificity, PPV and predicted negative values (NPV), while we were the first to evaluate P+P criteria of analytical reliability. Previously, we have evaluated sensitivity (0.66), specificity (0.80), PPV (0.10) and NPV (0.79) of RAST to soy in 143 children with AD[26], while the prevalence of RAST to food and Der p was as follows: egg 49%, CM 34%, soy 24%, wheat 22% and Der p 18%[26]. In addition, Table V[24] shows the criteria of analytical reliability of SPTs and RAST for CM and egg as regards immediate and total reactions, SPTs sensitivity is high for CM and egg, however specificity is lower than that of RAST for CM and egg, the SPT and RAST PPVs are equivalent, while SPT NPV results (79 for CM and 88 for egg) are better than RAST, especially for egg[24]. Since history is unreliable especially regarding the immediate reactions predictivity, challenge tests in children with positive SPTs should always be done with caution. The SPTs high NPVs permits to exclude immediate reactions following the challenge test. RAST sensitivity is lower than that of SPTs. RAST specificity is better than SPTs, however neither can be utilized at the clinical level. In addition RAST NPV is lower than that of SPTs and consequently scarcely useful for FA diagnosis. Its use should be limited to those cases in whom antihistamine administration cannot be discontinued or dermographism is remarkable or lichenification fails to allow SPTs evaluation[17].

In order to overcome such difficulties, the P+P test can have a high value as a screening test in children with possible sensitization to CM6. It is of note that in the 128 children

Table IV. Results of SPTs, P + Ps and OFCs in 58 children with food allergy.

Food	SPTs	P + P	OFCs
Cow milk	18	14	17
Egg	30	30	22
Wheat	16	12	16

Table V. Sensitivity, specificity and predictive accuracy of SPTs and RAST to cow's milk (CM) and egg in children with AD (immediate + late reactions).

	PREDICTIVE ACCURACY							
	Sensitivity		Specificity		Positive		Negative	
	SPT	*RAST*	*SPT*	*RAST*	*SPT*	*RAST*	*SPT*	*RAST*
CM	88	44	30	66	46	46	79	63
EGG	95	61	38	83	60	56	88	55

SPT = Skin prick test(s). From reference[24].

Table VI. Sensitivity, specificity and predictive accuracy of SPTs and RAST to cow's milk (CM) and egg in children with AD (immediate + late reactions).

	Nidina HA		Alimentum		Profylac	
	P + P	RAST	P + P	RAST	P + P	RAST
Specificity	0.69	0.22	0.89	0.89	0.80	0.63
Sensitivity	0.63	0.50	1	1	0	0
PPV	0.62	0.34	0.62	0.50	0	0
PPN	0.70	0.35	1	1	0.82	0.72

HF = Hydrolysate formula(s) PPV = Predictive value +, PPN = Predictive value. From reference[20].

with AD, the concordance between the P+P technique and the OFC test was poor, *especially* for orange and tomato (Table II)[19], considering that the first is rich of tyramine and the second of histamine. In this study, however, there was a very good agreement between OFCs and P+Ps (82.3%). Although the data outlined in Table IV show a good concordance between SPTs and P+Ps, applying the criteria of analytical reliability[25] we have found a good agreement between P+Ps and SPTs, but both lack sensitivity for wheat (Table III) and RAST (Table VI)[20]. P+Ps show also a good correlation with the OFC results. A recent comparison between P+Ps and RAST showed a moderate to good agreement10.

Several authors (Table I) have used P+P with good results, Rancé et al[27] have confirmed our previous results[18], and the present ones, that is fresh food extracts are more effective than commercial extracts in detecting IgE-mediated sensitization. They concluded that fresh foods should be used for primary testing when allergy to CM, egg and peanut was suspected[27]. Rosen et al[28] also suggested that the patients should be tested in the form that caused a reaction, that is in the form in which it was consumed. They observed that SPTs were negative in some patients using commercially available extracts, but were positive when SPTs were repeated with fresh foods[28]. Therefore FA cannot be excluded only because SPTs are negative, as shown by us in an infant with FA and negative SPTs. We performed a P+P with commercial fresh CM diluted 1:1 with distilled water: after a few minutes the infant had a wheal measuring 1 cm with a surrounding erythema of 2 cm.

A good agreement has been found between SAFT and P+P in 52 children (2-4 years of age) with AD[10]. Moreover, we can confirm a 90,3% concordance[27] between P+P and OFCs (Table IV).

In conclusion, P+Ps afford easier results that SPTs, and we expect that further data will confirm the effectiveness of P+Ps Their use for natural allergens could be of great help in clinical practice, in addition to being associated with no known risk of anaphylaxis[29]. However, it was shown that 6 infants less than 6 months of age out of 1.152 tested during three years (0.17% for each year) suffered from generalized allergic reactions after prick tests with fresh foods30. However, in the same period of time, we have done prick tests in at least 10,000 children, without seeing any generalized allergic reaction. Therefore allergists who cannot afford extracts, or who need a diagnosis at the bed of the child, can rely on an affordable, easily ready method. Hopefully most SPT problems will be overcome with recombinant allergens[31,32].

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