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Article type : Original Article: Food Allergy and Gastrointestinal Disease

Title:

Food-dependent NSAID-induced hypersensitivity reactions (FDNIH): unraveling the clinical features and risk factors

Short Title: Food-dependent NSAID-induced hypersensitivity reactions

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This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the [Version of Record](#). Please cite this article as [doi: 10.1111/ALL.14689](https://doi.org/10.1111/ALL.14689)

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Acknowledgments

RM-C is a recipient of a Juan Rodes fellowship (Carlos III Health Institute JR16/00016).

This work was supported by the Ministerio de Economía y Competitividad – Instituto de Salud Carlos III (FIS- PI11/01326 and FIS –PI16/00696), Spain.

Author Contributions:

JSL, RMC and JB designed the study. JSL and JB wrote de protocol and applied for ethical approval. JSL, GA, AGM, RCS, VC, MG and MP were involved in acquisition of data. JSL and JB wrote the first draft. RMC, MJT, ID, VC and CP were involved in critical review of the manuscript. JSL and JB are responsible for the final version. All authors revised and approved the submitted version of the manuscript.

Conflict of Interest

Dr. Sánchez-Lopez has nothing to disclose

Dr. Araujo has nothing to disclose

Dr. Cardona has nothing to disclose

Dr. Garcia-Moral has nothing to disclose

Dr. Casas-Saucedo has nothing to disclose

Dr. Guilarte has nothing to disclose

Dr. Torres has nothing to disclose

Dr. Doña has nothing to disclose

Dr. Picado has nothing to disclose

Dr. Pascal has nothing to disclose

Dr. Muñoz-Cano has nothing to disclose

Dr. Bartra has nothing to disclose

ABSTRACT

Background. In up to 70-80% of patients with a suspected non-steroidal anti-inflammatory drug hypersensitivity (NSAIDH) challenge tests with the culprit drug yield negative results. On the other hand, there could be a NSAIDH overdiagnosis when anaphylaxis is the clinical manifestation. We hypothesize that some negative NSAID challenge tests and an overdiagnosis of NSAIDH occurs in patients with food-dependent NSAID-induced hypersensitivity (FDNIH).

Methods. We studied 328 patients with a suspected acute NSAIDH. FDNIH was diagnosed in patients meeting all the following: 1) tolerance to the food ingested more temporally closed before the reaction, later the episode, 2) respiratory or cutaneous symptoms or anaphylaxis related to NSAID, 3) Positive skin prick test to foods and/or specific IgE to food allergens (Pru p 3, Tri a 19, Pen a 1) involved in the reaction and 4) Negative oral provocation test to the culprit NSAID.

Results. 199 patients (60%) were diagnosed with NSAIDH and 52 (16%) with FDNIH. Pru p 3 was involved in 44 cases (84.6%), and Tri a 19 in 6 cases (11%). FDNIH subjects were younger ($P<0.001$), with a higher prevalence of rhinitis ($P<0.001$) and previous food allergy ($P<0.001$), together with a higher proportion of subjects sensitized to pollens ($P<0.001$), and foods ($P<0.001$). Using just four variables (Pru p 3 and Tri a 19 sensitization, anaphylaxis and any NSAID different from pyrazolones), 95.3% of cases were correctly classified, with a sensitivity of 92% and specificity of 96%.

Conclusion. Evaluation of FDNIH should be included in the diagnostic work up of NSAIDH.

Key Words:

Food Allergy, Drug Allergy, NSAID

List of acronyms used in this article:

EAACI: European Academy of Allergy and Clinical Immunology

ENDA: European Network for Drug Allergy

FA: Food Allergy

FDNIH: Food-dependent NSAID-induced hypersensitivity

slgE: Specific Immunoglobulin E

LTP: Lipid Transfer Protein

NECD: NSAID-exacerbated cutaneous disease

NERD: NSAID-exacerbated respiratory disease

NIUA: NSAID-induced urticaria/angioedema

NSAID: Non-steroidal anti-inflammatory drug

NSAIDH: Non-steroidal anti-inflammatory drug hypersensitivity

OPT: Oral Provocation Test

OR: Odds Ratio

SNIRD: single NSAID-induced delayed hypersensitivity

SNIUAA: NSAID-induced urticaria/angioedema or anaphylaxis

SPT: Skin Prick Test

WDEIA: wheat dependent exercise induced anaphylaxis

INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs) are considered the most common drugs involved in hypersensitivity reactions in susceptible individuals (1,2). According to the latest classification for NSAID hypersensitivity from the European Network for Drug Allergy (ENDA) (1,2), NSAIDs hypersensitivity is classified as: 1) Non-immunologically mediated (cross-reactive), hypersensitivity reactions to NSAIDs which includes NSAID-exacerbated respiratory disease (NERD), NSAID-exacerbated cutaneous disease (NECD) and NSAID-induced urticaria/angioedema (NIUA), and 2) immunologically mediated (non-cross-reactive) hypersensitivity reactions to NSAIDs, which include the single NSAID-induced urticaria/angioedema or anaphylaxis (SNIUAA) and the single NSAID-induced delayed hypersensitivity (SNIRD) reactions (1,2).

Diagnosis of hypersensitivity reactions to NSAIDs is based on carefully obtained information of the patient's history with description of symptoms, timing of reaction, previous episodes potentially related to NSAIDs and underlying chronic comorbidities (rhinosinusitis, nasal polyps, asthma, and urticaria). In most cases, a drug provocation test remains the gold standard to confirm the diagnosis of NSAID hypersensitivity. However, provocation tests are not recommended in case of severe anaphylaxis (1,2).

Interestingly, in most studies, only 20-30% of patients with a previous history suggesting a NSAID-induced hypersensitivity reaction are finally classified according to the ENDA work up approach (3-8). The clinical history has a low predictive value because it may not include factors that can contribute to the reaction. This may be the case of patients FDNIH.

Food allergy (FA) has a prevalence of 2-5% of the general population (9, 10) and accounts for one-third to one-half of anaphylaxis cases (11-13). FA frequently depends on other concomitant factors (co-factors) such as the intake of NSAIDs or exercise. The World Allergy Organization, American Academy of Allergy, Asthma and Immunology, American College of Allergy, Asthma and Immunology and the European Academy of Allergy and Clinical Immunology (EAACI) Guidelines highlight the relevance of these co-factors in FA (10,14). Indeed, co-factors in general are reported to be relevant in 20-30% of anaphylactic episodes (15-18). NSAID intake has been reported to be present in up to 22% of food-induced anaphylactic shocks, representing a risk factor with an odds ratio higher than 11 (19). In some FDNIH reactions, NSAID is the only co-factor required to trigger or enhance the symptoms, such as urticaria or anaphylaxis (20-26). The spectrum of foods involved in FDNIH is wide (wheat, nuts, seeds, vegetables, shellfish, peanut) (19-29), highlighting wheat, plant-foods and shellfish as the most prevalent foods involved. Foods

involved in FDNIH also seem to have a geographical pattern. Whereas in Japan gliadins from wheat are involved in most cases (20,26,27), lipid transfer proteins (LTPs) from plant foods have been recently reported as major culprit allergens in the Mediterranean area (21-24).

The aims of this study were: 1) to unravel FDNIH when NSAID hypersensitivity is suspected, 2) to define the clinical characteristics / clinical phenotype of FDNIH, and 3) to establish risk factors involved in FDNIH to differentiate these cases among all patients with suspected NSAID hypersensitivity.

PATIENTS AND METHODS

Patients

A prospective multicenter study was carried out in the Hospital Clinic and Hospital Vall d'Hebron, both in Barcelona, Spain. The study was approved by the Hospital Clinic and the Hospital Vall d'Hebron Ethics Committees and written informed consent was obtained from all patients. All consecutive adults (n=328) with a suspicion of acute NSAID hypersensitivity referred to our allergy departments from June 2012 to July 2015 were recruited. Recommendations from ENDA guidelines were followed to diagnose NSAID hypersensitivity (1,2). In order to identify FDNIH, all patients underwent a thorough evaluation of food allergy as shown in figure 1. As an exception to ENDA guidelines, patients referred for anaphylaxis were challenged with the NSAID involved in the reaction when FDNIH was suspected based on the detection of IgE sensitization to any food ingested before the reaction. At the end, patients were diagnosed with FDNIH when they met all the following criteria:

- 1) Mild reaction (oral allergy syndrome or contact urticaria) or tolerance to the foods involved in the reaction - after the episode -, in the absence of the NSAID.
- 2) Systemic allergic reaction -urticaria, angioedema, bronchospasm or anaphylaxis; the latter, according to EAACI guidelines definition (2)- in the context of food and NSAID intake (maximum interval of 6h between food ingestion and reaction and 8h between NSAID intake and reaction).
- 3) Positive skin prick test (SPT) and/or specific IgE (slgE) to any food ingested before the reaction and/or gliadin, LTP or tropomyosin (20-22,25).
- 4) Negative oral provocation test (OPT) to the NSAID/NSAIDs involved in the reaction/s;

In the cases identified as FDNIH, it was also investigated if patients had full tolerance to the suspected food involved in the absence of an NSAID. These cases were considered as "ON/OFF

effect", that is, in the presence of a cofactor, a systemic reaction occurs, while in the absence of it there is full tolerance of the same food.

For the purpose of the study, all patients in whom FDNIH was ruled out were considered as the control group.

Demographic data, previous food allergy based on a consistent clinical history, previous reactions related to NSAIDs, eliciting NSAID, reported symptoms with the NSAID and related comorbidities (chronic rhinosinusitis, asthma, urticaria) were collected. Reported symptoms were classified as urticaria and/or angioedema, rhinitis and/or asthma and anaphylaxis, grouping them in 3 categories, cutaneous, respiratory and anaphylaxis to facilitate interpretation of data. In the clinical evaluation of any suspected reaction with an NSAID, patient was asked about different time intervals around the reaction: a) time between NSAID and reaction, b) time between last food intake and reaction and c) time between NSAID and last food intake were also evaluated. In the case of patients with multiple episodes, all the available data was considered for the evaluation of frequencies and time-interval means. In cases where the patient couldn't remember the data, it was not taken into account.

Skin prick tests

SPT were performed with a panel of commercial allergenic extracts (Laboratorios LETI, Madrid, Spain), of the most prevalent food allergens in adults in our area (peach, apple, melon, kiwifruit, walnut, hazelnut, peanut, maize, wheat, soy, chickpea, lentil, mustard, lettuce, tomato, green bean, cod, shrimp, anisakis), Gliadin (5mg/ml) (Laboratorios LETI, Madrid, Spain) and Pru p 3 (100 µg/ml) (Bial-Aristegui, Bilbao, Spain). Foods not included in the standard panel and involved in the reaction were also tested with a commercial extract if available or by prick-prick. SPT were also performed with a panel of commercial glycerinated allergenic extracts of the most prevalent aeroallergens in our area, including biologically standardized allergenic extracts of *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, *Alternaria alternata*, *Aspergillus fumigatus*, *Cladosporium herbarum*, *Penicillium notatum*, *Blatella orientalis*, *Lolium perenne*, *Parietaria judaica*, *Artemisia vulgaris*, *Olea europea*, *Platanus acerifolia*, *Cupressus arizonica*, *Betula verrucosa*, dog and cat dander (Laboratorios LETI, Madrid, Spain) and palm profilin (Pho d 2, 50 µg/ml) (ALK-Abelló, Madrid, Spain). SPT were performed on the volar surface of the forearm using a 1 mm single peak lancet (Alk-Abelló, Spain). Histamine hydrochloride (10mg/ml) and saline solution were used as positive and negative controls, respectively. The SPT was considered positive if the diameter was greater than 3 mm compared to the negative control.

Specific IgE determination

The individual sera of all recruited patients were tested for IgE to rTri a 19, rPru p 3 and rPen a 1/nPen m 1 by means of immunoassay (ImmunoCAP, Thermo Fisher Scientific, Uppsala, Sweden) or allergen microarray immunoassay (ImmunoCAP ISAC; Thermo Fisher scientific, Uppsala, Sweden). The cutoff value for sIgE was 0.10 kU/L (ImmunoCAP) and 0.3 ISAC Standardized Unit (ISU) (ImmunoCAP ISAC). These allergens were chosen for their implication as cofactors in FDNIH.

NSAID evaluation tests

Skin tests with the drugs involved were carried out, if available, following ENDA recommendations (1,2). In case of a negative skin test, an oral provocation test (OPT) with the drug involved was performed according to ENDA recommendations (1,2). In the case that different NSAIDs were involved in different episodes, the patient was challenged with all of them with at least 1-week interval.

Statistical analysis

Continuous variables were expressed as means and standard deviations (SD) and categorical variables were expressed as frequencies (percentages). Continuous data were compared using the Mann-Whitney *U*-test, and categorical data were compared using the χ^2 test (and Fisher's exact test when appropriate). A logistic regression analysis was used to examine the relationships between the presence of FDNIH and multiple risk factors. All variables collected in the database were analyzed as potential risk factors in the logistic regression analysis. Statistical significance was taken as a 2-sided *p* value of less than .05. SPSS software (version 18.0; SPSS, Chicago, Ill) was used in the analyses.

RESULTS

Following the current ENDA recommendations and our specific approach to explore FDNIH, the 328 patients were finally diagnosed as follows: 97 NIUA (29.6%), 20 NECD (6.1%), 40 SNIUAA (12.2%), 42 NERD (12.8%) and 52 FDNIH (15.9%). In 77 cases (23.5%) both FDNIH and NSAID hypersensitivity were ruled out. As indicated before, all patients in whom FDNIH was ruled out were considered as the control group. Demographic characteristics showed that FDNIH subjects were significantly younger than the control group ($P<0.001$), with a higher prevalence of rhinitis ($P<0.001$) and previous history of food allergy ($P<0.001$), together with a higher proportion of subjects sensitized to pollens ($P<0.001$), animal dander ($P=0.013$) and foods ($P<0.001$) (table 1).

Sixty-seven patients were initially considered as candidates to be FDNIH due to the potential implication of both food and NSAID in the reaction. Among them, 15 cases were ruled out because of a positive test (cutaneous or OPT) with the culprit NSAID. LTP (14 cases, 93.3%) and gliadin (1 case, 6.7%) were the food allergens involved in these patients.

Food elicitors

The food elicitors were varied, mainly fruits, vegetables and wheat. Overall, LTP was involved in 44/52 cases (84.6%) and gliadin in 6/52 cases (11%). Additionally, among the LTP-sensitized subjects, 75% were sensitized to 3 or more LTP-containing foods and 50% were also sensitized to plane tree and/or mugwort pollen, pointing out the importance that LTP syndrome may have in FDNIH. Pru p 3 and gliadin sensitization were detected by SPT in all cases except for one gliadin case that was detected by serum sIgE. Although in 16 cases, food was not clearly identified by the patient, LTP sensitization was identified in all but one and 5 of them the clinical manifestation was anaphylaxis. Additionally, these patients didn't introduce any change in their diet and didn't present any new reaction in the absence of NSAID and, according to inclusion criteria, all of them tolerated later the NSAID involved in the reaction. Although Pen a 1 sensitization was detected in 15 out of 328 patients included, none of them were related to FDNIH in our population. A full description of all FDNIH cases, including the NSAID/s and foods involved, the symptoms during the reaction and the individual sensitization profile, is provided in table 2.

ON/OFF effect

The "ON/OFF effect" refers to the situation where patients fully tolerate a food when ingested alone but manifest a systemic reaction after its ingestion in the presence of a cofactor. Data about the food/s involved were available in 36 out of 52 patients. Among them, twenty-five (69.4%) were ON/OFF, while the others had mild symptoms when ingesting the causative food alone. Among the ON/OFF-effect group, six (24%) were induced by gliadin and 18 cases (72%) by an LTP containing food. In one case neither gliadin nor LTP were the responsible allergens. It is important to note that all patients allergic to gliadin behaved as ON/OFF. On the other hand, most LTP-allergic patients that had an ON/OFF effect with a certain plant food, had also mild symptoms (oral and contact urticaria) with other plant foods.

NSAIDs involved

Propionic acids were the NSAIDs most frequently involved in FDNIH reactions (79%), followed by aspirin (25%). Aryl acetic acids, pyrazolone and paracetamol were significantly less involved in FDNIH than in the control group ($P=0.018$, $P<0.001$ and $P=0.016$, respectively) (table 3).

Regarding the number of different NSAID families involved in the reactions per patient, it was significantly lower in FDNIH (1.25 ± 0.6) compared to the control group (1.95 ± 1 ; $P < 0.001$).

Symptoms

Regarding symptoms, 27/52 (52%) of FDNIH cases presented with anaphylaxis, while in the control group anaphylaxis only represented 9.4% (26/276; $P < 0.001$). These episodes of anaphylaxis were mediated by LTP in 23 cases (85.2%) and by gliadin in 2 (7.4%). No FDNIH patients had respiratory symptoms as isolated manifestation (table 2). On the other hand, the most frequent manifestations in the control group were cutaneous (203/276, 73.5%), followed by respiratory (47/276, 17%) symptoms. Anaphylaxis in the control group (26/276, 9.4%) occurred mainly in single NSAID hypersensitivity (15 cases), followed by cross-reactive NSAID hypersensitivities (10 cases). One reaction was finally classified as idiopathic anaphylaxis, as neither the NSAID nor any other factor could be identified as the elicitor.

Time intervals

The analysis of the time intervals between the intake of the NSAID, last food ingestion and the onset of the reaction are shown in table 4. In most FDNIH cases, NSAID administration took place within 2 hours prior to the reaction (81%). Mean time was 92 ± 75 minutes, not different to the control group (94 ± 135 minutes); however, stratification of time intervals showed that most reactions in the control group appeared in the first 30 minutes after drug intake (52.2% vs. 27.7%; $P = 0.002$). Regarding the time elapsed between the last food ingestion and the reaction, mean time was 110 ± 83 minutes for FDNIH, while in the control group it was more than double (248 ± 211 minutes; $P < 0.001$); most reactions in the FDNIH appeared in the first 2h after food ingestion (table 4). In most FDNIH cases, food ingestion was prior to NSAID intake (82%), similar to the control group (86%). Food ingestion and NSAID intake were very close to each other in FDNIH, with a mean time of 14 ± 77 minutes. In fact, both events were separated by an interval of 2h or less in 97.7% of FDNIH cases. This finding clearly contrasts with that found in the control group, where the mean time between food and NSAID intake was 132 ± 200 minutes ($P < 0.001$).

Risk factors for FDNIH: univariate and multivariate logistic regression analysis

In the univariate logistic regression analysis (table 5A), FDNIH was found to be mainly associated with LTP (OR=83.8; $P < 0.001$) and gliadin sensitization (OR=21.3; $P < 0.001$). Other risk factors were pollen sensitization and anaphylactic reaction, while cutaneous reaction or being the NSAID involved an aryl acetic or a pyrazolone resulted protective (table 5A). The rest of variables analyzed were not significant.

In the multivariate logistic regression analysis (table 5B), pollen sensitization and aryl acetic implication in the reaction lost significance, so they were excluded by using a forward stepwise procedure. Having an anaphylactic reaction was exclusive to having a cutaneous reaction, so only anaphylactic reaction was left in the multivariate analysis. Using 4 variables, LTP and gliadin sensitization, anaphylaxis and NSAID involved other than pyrazolones, our model was capable of correctly classifying 95.3% of patients into the FDNIH group, with a sensitivity of 92% and specificity of 96%.

DISCUSSION

Previous studies have shown that the application of ENDA's diagnostic approach to NSAID hypersensitivity results in the exclusion of NSAIDs as the trigger in up to 80% of assessed patients (3-8).

We hypothesized that some of the excluded cases are patients with FDNIH that are not diagnosed because the ENDA protocol does not consider that NSAIDs may act as a cofactor (and not as a sole trigger), and therefore does not include the assessment of food allergy in their work up.

In this study we have carried out a characterization of FDNIH, searching for markers that could help in the diagnosis and management of these patients. An initial remarkable finding is that 16% of patients suspected of NSAID hypersensitivity were finally diagnosed as FDNIH, with LTP being the main food allergen involved. The potentially relevant role of the association between hypersensitivity to LTP and NSAID had already been suggested by A. Romano (24). The main consequence that may follow from not considering this entity is that patients are still at risk of a new reaction. Because food allergy has not been considered and NSAID hypersensitivity has been ruled out, neither the food, nor the NSAID are avoided and therefore new hypersensitivity reactions may occur.

The characterization of the population studied shows that in our area, LTP is the main responsible/elicitor of FDNIH, with gliadin following far behind. The key role played by LTP in our patients is in line with previous studies that have shown the high prevalence of plant food allergy associated with NSAIDs as cofactors in the Mediterranean area (21-23), but contrasts with other articles where gliadin is the most frequent responsible allergen (20, 26, 27). The systematic use of both SPT and sIgE to Pru p 3 (LTP) and Tri a 19 (gliadin) in our study showed that both methods are similarly valid in the detection of these sensitizations. Although tropomyosin has

been identified as one of the responsible for FDNIH (25), in our series there were no cases involving that protein.

Although, the LTP syndrome (considered when an LTP-sensitized patient displays reactivity to several taxonomically unrelated plant-foods containing LTP) has rarely been reported in patients from other geographical regions, recent studies have shown that the prevalence of patients diagnosed with LTP syndrome is much higher than previously reported, when the Pru p 3 is systematically included in the work up of patients with history of food-induced allergic reactions (29-36). The spectrum of food allergens involved in FDNIH may vary depending on the ecological characteristics and dietary habits of the studied populations (19-29). Moreover, the potential implication in FDNIH of other predominant pan-allergens, such as profilins or PR-10, frequently present in other geographical areas, should not be overlooked. Allergic reactions caused by these proteins are usually mild, but they can also precipitate anaphylaxis when associated with a cofactor such as exercise (37). Whether severe allergic reactions can also result from the combined effect of these allergens and NSAIDs remains to be thoroughly explored.

Although less frequently than in the case of profilin, most individuals sensitized to Pru p 3 are asymptomatic or paucisymptomatic (21-23, 38) and only the intake of an NSAID reveals the key role played by food sensitization in the hypersensitivity reaction (21-23). The limited clinical expression of food sensitization can easily lead the evaluating physician to discard its role in the reaction.

Considering the time intervals is also important in the suspicion of FDNIH, because most of the FDNIH reactions (>90%) occur within the first 3h after food and NSAID ingestion, and no reaction was detected after the 5th hour.

Interestingly, almost 70% of FDNIH patients experienced an ON/OFF effect in which the offending food was perfectly tolerated in the absence of NSAID intake. This phenomenon is well-known in wheat dependent exercise induced anaphylaxis (WDEIA) (39). It is likely that both entities share common pathophysiologic pathways. Currently, two main hypotheses have been proposed to explain FDNIH. One theory suggests that NSAIDs, increase the permeability of the intestinal barrier causing a major absorption of the culprit allergen with mast cells playing a complementary role (8,37). Another hypothesis suggests that NSAIDs have a direct effect on mast cells and basophils, amplifying their degranulation/activation (39,40). Interestingly, aspirin potentiates the effect of exercise in WDEIA, a finding that further supports a common underlying pathophysiologic mechanism in WDEIA and FDNIH (41,42).

Numerous NSAIDs were involved in FDNIH and in some patients more than one NSAID triggered the hypersensitivity reaction, this could be considered as a class effect. These observations indicate that the underlying mechanism may be related with some characteristic shared by all NSAIDs, such as cyclooxygenase inhibition. Interestingly, true NSAID hypersensitivity is also present in patients with food allergy. This is not an unexpected finding given the high prevalence of NSAID hypersensitivity and food allergy in the population. This observation supports the individualized assessment of both NSAIDs and food allergens in patients with history of NSAID hypersensitivity.

The percentage of patients with NSAID hypersensitivity resulting from an IgE-mediated mechanism is relatively low compared with some (6,8) but not all studies (3,7). These differences can be explained, at least in part, by differences in the demographic (children vs adults) and clinical conditions of the studied populations. That could explain why pyrazolone derivatives are much more prevalent in the control group than in the FDNIH, since this group is the most frequently involved in single NSAID hypersensitivity reactions in Spain (43, 44).

The multivariate analysis has helped to identify some risk factors for FDNIH. With 4 variables, LTP or gliadin sensitization, anaphylactic reaction and the NSAID involved in the reaction different from a pyrazolone, we correctly classified 95.3% of cases, with a sensitivity of 92% and specificity of 96%. Thus, in the evaluation of hypersensitivity reactions, the presence of these risk factors should alert about the risk of suffering FDNIH.

Our study has some limitations. The high frequency of LTP sensitization in our population may limit the extrapolation of our findings beyond the Mediterranean area. However, sensitization to Pru p 3 has recently been reported in other geographical areas (30,32,34,35,36,45), and whether FDNIH also occurs associated with LTP in these other regions remains to be thoroughly assessed. Indeed, gliadin has also been considered a food allergen with limited geographical distribution. Interestingly, our study shows that gliadin can be involved in FDNIH in a region with apparently low prevalence of sensitization. These findings support the notion that the involvement of some food allergens in FDNIH cannot be excluded on the basis of their low prevalence in the studied population. Another limitation of our study is the lack of food challenge in combination with the NSAID. The diagnosis of FDNIH has been based on a thorough assessment of clinical history supported by SPTs and/or sIgE analysis. Previous reported studies using challenge with food and cofactor in WDEIA, show that diagnosis is only reached in 30% of the cases, and it implies many risks for the patient (39,46). In fact, several cofactors may be necessary to elicit the reaction in challenge tests, and a high concentration of plasma gliadin is required to trigger

symptoms (41,42,47). Since these patients may be at a high risk of anaphylaxis, our development of an evidence based diagnostic algorithm (Figure 1) can greatly support the diagnosis of FDNIH.

In summary, FDNIH accounts for a considerable percentage of patients with clinical history of NSAID hypersensitivity. LTP and gliadin have been identified as the main risk factors to consider, and for that reason, FDNIH must be considered and food allergy tests must be included in the diagnostic work up of patients with clinical history of NSAID hypersensitivity. Our proposed algorithm provides a comprehensive way to tackle the differential diagnosis of NSAID hypersensitivity and helps to identify FDNIH patients among them.

Table 1. Demographic characteristics of FDNH subjects and comparison with the control group.

	FDNIH		Control		p-value
	n°	%	n°	%	
Total n°	52	19	276	81	
Gender, female	35	67.3	173	62.7	>0.05
Age (y), mean (SD)	42.31 (11)		47.95 (15)		<0.001
Rhinitis	38	73.1	136	49.8	<0.001
Asthma	10	19.2	68	24.9	>0.05
Previous diagnosis of FA *	45	86.5	29	10.6	<0.001
SPT sensitization	53	100	139	50.9	<0.001
Inhalants, any	44	82.7	131	48	<0.001
Pollen	35	67.3	74	27.4	<0.001
HDM	26	50	97	35.9	>0.05
Animal dander	15	28.8	39	14.4	0.013
Moulds	5	9.6	12	4.4	>0.05
Food, any	51	98.1	52	19	<0.001
Positive food SPTs, mean (SD)	4.94 (3)		0.42 (1.3)		<0.001

FDNIH, Food-dependent NSAID induced hypersensitivity; *SD*, standard deviation; *SPT*, skin prick test; FA: food allergy. *By consistent clinical history.

Table 2. Clinical characteristics of FDNH patients: NSAID involved, Food involved, Symptoms and IgE sensitizations.

Patient	NSAIDs	n° episodes	Symptoms	Foods involved	“ON/OFF effect”	Previous food allergy	Food SPTs	Aeroallergen SPTs	Pru p 3 slgE*	Tri a 19 slgE*	Pen a 1 /Pen m 1 slgE*
1	Aspirin	1	AF	pn	No	Yes	Pru p 3, pe, pn	hdm, gr, ol	4.54	0.01	0.01
2	Aspirin	1	AF	mz-based snack	Yes	Yes	Pru p 3, mz, cp	hdm	3.45	0.01	0.01
3	Ibuprofen	1	AF	gb, ap	No	Yes	Pru p 3, ap	hdm, gr, ol, cd	0.24	0.01	0.01
4	Ibuprofen	1	U	wh, wm	Yes	Yes	Pru p 3, hz, kw, mz, pn, mu, wm, wh	mw	12.90	0.01	0.01
5	Ibuprofen	1	AF	le	Yes	Yes	Pru p 3, kw, le, mz, gb	pl, cy	1.09	0.01	0.01
6	Dexketoprofen	1	U	n/a	n/a	Yes	Pru p 3, mz, cp, wh, pn	hdm	3.22	0.02	0.01
7	Ibuprofen, aspirin	2	U	wh	Yes	No	Sh, gl	hdm	0.02	0.75	0.01
8	Diclofenac	1	AF	n/a	n/a	Yes	Pru p 3, pe, hz, mz, mu	mw, pl, ol, cy	0.27	0.01	0.01
9	Ibuprofen	1	U	ap	Yes	Yes	Pru p 3, ap	-	0.35	0.01	0.01
10	Aspirin	1	AF	Veggies	No	Yes	Pru p 3, mz, kw, hz, pe, le	-	0.26 ISU	0 ISU	0 ISU
11	Naproxen	4	AE	Veggies	No	Yes	Pru p 3, mz, le	hdm	na	na	na
12	Aspirin	1	AE	n/a	n/a	Yes	Pru p 3, hz, kw, pe, mz, wh, pn, mu	hdm, dd, cd, gr, wp, mw, pl	17.7	na	0.01
13	Ibuprofen	2	U/AE	wh	Yes	Yes	gl, ak, sh	hdm	na	0.5	0.01
14	Ibuprofen	4	AE	n/a	n/a	Yes	Pru p 3, pe, hz, pn, gb	-	4.44	0.01	0.01

15	Ibuprofen	1	AF	to, le	No	Yes	Pru p 3, hz, kw, pe, mz, cp, pn, gb, le, sh	hdm, ol, cd, dd	5.3 ISU	0 ISU	0 ISU
16	Ibuprofen, aspirin, paracetamol, diclofenac	4	AF	wh	Yes	Yes	gl	-	0.01	30.8	0.01
17	Ibuprofen, pyrazolone	2	U/AE	n/a	n/a	Yes	Pru p 3, pe, kw	gr, pl, wp	0.29	0.01	0.01
18	Aspirin	1	U/AE	ch	Yes	Yes	Pru p 3, ch, pe, ml, sh	hdm	0.46	0.01	0.01
19	Ibuprofen	1	U/AE	wn	Yes	Yes	Pru p 3, hz, pn, wn, pe, so, gb	pl, wp, gr, cd, dd, ol, mw	0.6 ISU	0 ISU	0 ISU
20	Dexketoprofen	1	U	n/a	n/a	Yes	Pru p 3, wh, mz, hz, pn, wn	mw	13	0.01	0.01
21	Aspirin	1	U	n/a	n/a	Yes	Pru p 3, pe, kw, mz, pn, sh, gb	-	11.30	0.01	0.01
22	Ibuprofen	2	AE	n/a	n/a	Yes	Pru p 3, sh	hdm, alt, ol	1.79	0.01	0.11
23	Ibuprofen, dexketoprofen	2	AF	n/a	n/a	Yes	Pru p 3, hz, pe	hdm, mw, pl	1.19	0.01	0.01
24	Ibuprofen, dexketoprofen	2	AF	wh	Yes	No	gl	hdm, pl	0.01	0.41	0.01
25	Ibuprofen	1	AF	ch	No	No	Pru p 3, pn, ap, ch, pe, gb	hdm, dd, cd	na	na	0.01
26	Ibuprofen,	2	U	wh	Yes	No	gl	dd, ol, pl, gr	0.01	3.73	0.01

	diclofenac										
27	Ibuprofen	1	AF	le, to	Yes	Yes	Pru p 3, hz, wn, pe, pn, cp, le, to	hdm, dd, cd, pl, wp	2.2 ISU	0 ISU	0 ISU
28	Ibuprofen	1	AF	le, to	No	Yes	Pru p 3, sf, wn, to, ln	pl, mw	0.3 ISU	0 ISU	0 ISU
29	Diclofenac	1	AF	le, gr	Yes	Yes	Pru p 3, hz, pn, wn, pe, cp, ml, le, to, wh, mu, ln	hdm, pl, dd, gr	1.9 ISU	0 ISU	0 ISU
30	Aspirin	1	AF	pe	Yes	No	Pru p 3, hz, pe, av, le, to, wh, gl, cd, mu, ak, wn, pn	-	na	na	na
31	Ibuprofen	2	U/AE	ap	Yes	No	Pru p 3, hz, wn, ap, pe, gb	dd, cd, cy, ol, pl, gr	na	na	na
32	Ibuprofen	1	U/AE	le	Yes	No	Pru p 3, hz, pn, wn, ml, kw, pe, le, ln	dd, pl	2.14	0.01	0.01
33	Ibuprofen, aspirin	3	AF	pe	No	Yes	Pru p 3, wn, pn, pe, ap, mu	pl, mw	12.5	0.01	0.01
34	Naproxen	1	AF	le, ba	Yes	Yes	Pru p 3, hz, pn, pe, le	-	na	na	na
35	Ibuprofen, aspirin	2	AF	gluten- free pasta	No	Yes	Pru p 3, hz, pn, kw, pe, mz, wh, mu, sh, ml, gb	hdm, gr, mw, ol, pl, cy, alt, cla, cd, dd, bi, Pho d 2	16.30	0.02	0.01
36	Ibuprofen	2	AF	n/a	n/a	Yes	Pru p 3, hz, kw, pe, mz, wh, cp, pn, mu, gb	hdm, mw, pl, cy	>100	0.02	0.01
37	Ibuprofen,	3	U/AE	n/a	n/a	Yes	Pru p 3, sh, pe, mz	wp, cd, dd,	0.70	0.01	0.01

	aspirin							Pho d 2			
38	Ibuprofen	3	U/AE	to	Yes	Yes	Pru p 3, hz, kw, pe, pn, gb, le, mz, cp, to	hdm, gr, wp, mw, ol, pl	23.8	0.05	0.01
39	Ibuprofen	1	AF	pe	Yes	Yes	Pru p 3, hz pe, mz, wh, sh, ml	pl, cy, alt, Pho d 2	1.35	0.01	0.01
40	Ibuprofen, aspirin	3	U/AE	le	Yes	Yes	Pru p 3, le, pe, mz, sh	wp, cd, dd, Pho d 2	0.70	0.01	0.01
41	Naproxen	1	U	cp	Yes	Yes	Pru p 3, cp, kw, pn	-	0.01	0.01	0.01
42	Dexketoprofen	1	AF	n/a	n/a	Yes	Pru p 3, pe, mz, pn, mu, cd	hdm, gr, mw, ol, pl, cd, dd	9.89	0.01	0.01
43	Naproxen	5	U/AE	n/a	n/a	Yes	Pru p 3, hz, kw, pe, wh, pn, mu, ml, gb	hdm, gr, pl, wp, cd, dd	4.3 ISU	0 ISU	0 ISU
44	Diclofenac	20	U/AE	wh	Yes	Yes	-	wp, ol, pl, cy	0.08	13.70	0.01
45	Ibuprofen	3	U	n/a	n/a	Yes	Pru p 3, kw, mz, wh, pn, gb	-	na	na	na
46	Dexketoprofen	1	AF	le	Yes	Yes	Pru p 3, hz, pe, mz, cp, pn, mu, gb	hdm, gr, mw, Pho d 2	14.20	0.01	0.01
47	Ibuprofen	1	AF	le, to	No	Yes	Pru p 3, hz, kw, le, pe, mz, wh, cp, pn, mu, ml, gb	mw, pl, cy	11.10	0.01	0.01
48	Pyrazolone	2	U	n/a	n/a	Yes	Pru p 3	wp, pl, cd	2.13	0.09	0.01
49	Ibuprofen	1	AF	ba, av	Yes	Yes	ba, av	hdm	0.01	0.01	0.01
50	Ibuprofen	2	AF	le, ln, gr	Yes	Yes	Pru p 3, hz, kw, le, pe,	hdm, gr, wp,	14.80	0.01	0.01

							mz, pn, mu, sh, gb	ol, cy, alt, cla, dd, bi, Pho d 2			
51	Ibuprofen	3	AF	n/a	n/a	Yes	hz, kw, mz, wh, pn, mu, ml	hdm, wp, cy, alt, cla	0.01	0.01	0.01
52	Ibuprofen	1	AF	pe	No	Yes	Pru p 3, hz, kw, pe, mz	hdm	21.70	0.01	0.01

NSAID, non-steroidal anti-inflammatory drug; SPT, skin prick test; na, not available. *Expressed in kU/L unless indicated.

Symptoms: AE: angioedema, AF: anaphylaxis, U: Urticaria

Aeroallergens: alt: *Alternaria spp*, bi: birch, cla: *Cladosporium spp*, cy: cypress, cd: cat dander, dd: dog dander, gr: grass, hdm: house dust mites, mw: mugwort, ol: olive, pl: plane tree, wp: wall pellitory. “-”: negative

Foods: ak: anisakis, ap: apple, av: avocado, ba: banana, cd: cod, ch: cherry, cp: chickpea, gb: green bean, gl: gliadin, hz: hazelnut, kw: kiwi, le: lettuce, ln: lentil, ml: melon, mu: mustard, mz: maize, pe: peach, pn: peanut, sf: sunflower seed, sh: shrimp, so: soy, to: tomato, wh: wheat, wm: watermelon, wn: walnut.

Table 3. NSAIDs involved in the FDNIH reactions

NSAID	FDNIH (n=52) n (%)	Control (n=276) n (%)	p-value
Propionic acids	41 (78.8)	192 (69.6)	>0.05
Aspirin	13 (25)	102 (37)	>0.05
Aryl acetic acids	5 (9.6)	67 (24.3)	0.018
Pyrazolone	2 (3.8)	85 (30.8)	<0.001
Paracetamol	1 (1.9)	37 (13.4)	0.016
Coxibs	0	13 (4.7)	>0.05
Oxicams	0	11 (4)	>0.05

NSAID, non-steroidal anti-inflammatory drug; FDNIH, Food-dependent NSAID induced hypersensitivity

Table 4. Characteristics of the time intervals between drug administration, food ingestion and onset of the reaction in FDNIH and control group

Table 4A. Time intervals between drug administration and onset of the reaction in FDNIH and control group.

	FDNIH	Control group	<i>P</i>
Mean±SD, minutes	93±76	94±135	>0.05
≤30 minutes; n (%)	13 (27.7)	107 (52.2)	0.002
31-60 minutes; n (%)	12 (25.5)	37 (18)	>0.05
61-120 minutes; n (%)	13 (27.7)	25 (12.2)	0.008
121-180 minutes; n (%)	5 (10.6)	11 (5.4)	>0.05
181-240 minutes; n (%)	1 (2.1)	8 (3.9)	>0.05
241-300 minutes; n (%)	3 (6.4)	1 (0.5)	0.021
301-360 minutes; n (%)	0	2 (1)	>0.05
>360 minutes; n (%)	0	14 (6.8)	>0.05

FDNIH, Food-dependent NSAID induced hypersensitivity

Table 4B. Time intervals between last food ingestion and onset of the reaction in FDNIH and control group.

	FDNIH	Control group	<i>P</i>
Mean±SD, minutes	110±83	248±211	<0.001
≤30 minutes; n (%)	11 (24.4)	16 (14)	>0.05
31-60 minutes; n (%)	7 (15.6)	21 (18.4)	>0.05
61-120 minutes; n (%)	15 (33.3)	18 (15.8)	0.014
121-180 minutes; n (%)	8 (17.8)	10 (8.8)	>0.05
181-240 minutes; n (%)	1 (2.2)	3 (2.6)	>0.05
241-300 minutes n (%)	2 (4.4)	5 (4.4)	>0.05
301-360 minutes; n (%)	1 (2.2)	5 (4.4)	>0.05
>360 minutes; n (%)	na	36 (31.6)	<0.001

FDNIH, Food-dependent NSAID induced hypersensitivity

Table 4C. Time intervals between last food ingestion and drug administration in FDNIH and control group.

	FDNIH	Control group	<i>P</i>
Mean±SD, minutes	14±77	132±200	<0.001
≤30 minutes; n (%)	32 (72.7)	51 (44.7)	0.002
31-60 minutes; n (%)	4 (9.1)	10 (8.8)	>0.05
61-120 minutes; n (%)	7 (15.9)	18 (15.8)	>0.05
121-180 minutes; n (%)	0	4 (3.5)	>0.05
181-240 minutes; n (%)	0	4 (3.5)	>0.05
241-300 minutes; n (%)	1 (2.3)	5 (4.4)	>0.05
301-360 minutes; n (%)	0	2 (1.8)	>0.05
>360 minutes; n (%)	0	20 (17.5)	0.003

FDNIH, Food-dependent NSAID induced hypersensitivity

Table 5. Univariate (A) and multivariate (B) logistic regression for diagnosing FDNIH when an acute NSAID hypersensitivity reaction is suspected (n=328).

Table 5A. univariate analysis

Risk factors	Odds ratio	95% CI	p-value*
LTP sensitization	83.8	34-206	<0.001
Gliadin sensitization	21.3	4.3-106	<0.001
Anaphylactic reaction	10.4	5.2-20.5	<0.001
Pollen sensitization	5.5	2.9-10.3	<0.001
Cutaneous reaction	0.33	0.19-0.61	<0.001
Involved NSAID group:			
- Aryl acetics	0.33	0.13-0.87	0.025
- Pyrazolones	0.09	0.02-0.38	0.001

*Wald test. Only p-value<0.05 are reported.

CI, confidence interval; *LTP*, lipid transfer protein; *NSAID*, non-steroidal anti-inflammatory drug.

Table 5B. Multivariate analysis

Risk factors	Adjusted Odds ratio	95% CI	p-value*
LTP sensitization	205	51-819.8	<0.001
Gliadin sensitization	117	15-917	<0.001
Anaphylactic reaction	8.54	1.9-37.3	0.004
Involved NSAID group:			
- Pyrazolones	0.034	0.004-0.28	0.002

*Wald test. Risk factors associated with FDNIH in the univariate analysis (p<0.05) are included in the multivariate analysis. Automatic forward stepwise procedure was used for model selection. As anaphylaxis and cutaneous reaction were exclusive to each other, cutaneous reaction was removed from the selected model. CI, confidence interval; *LTP*, lipid transfer protein; *NSAID*, non-steroidal anti-inflammatory drug.

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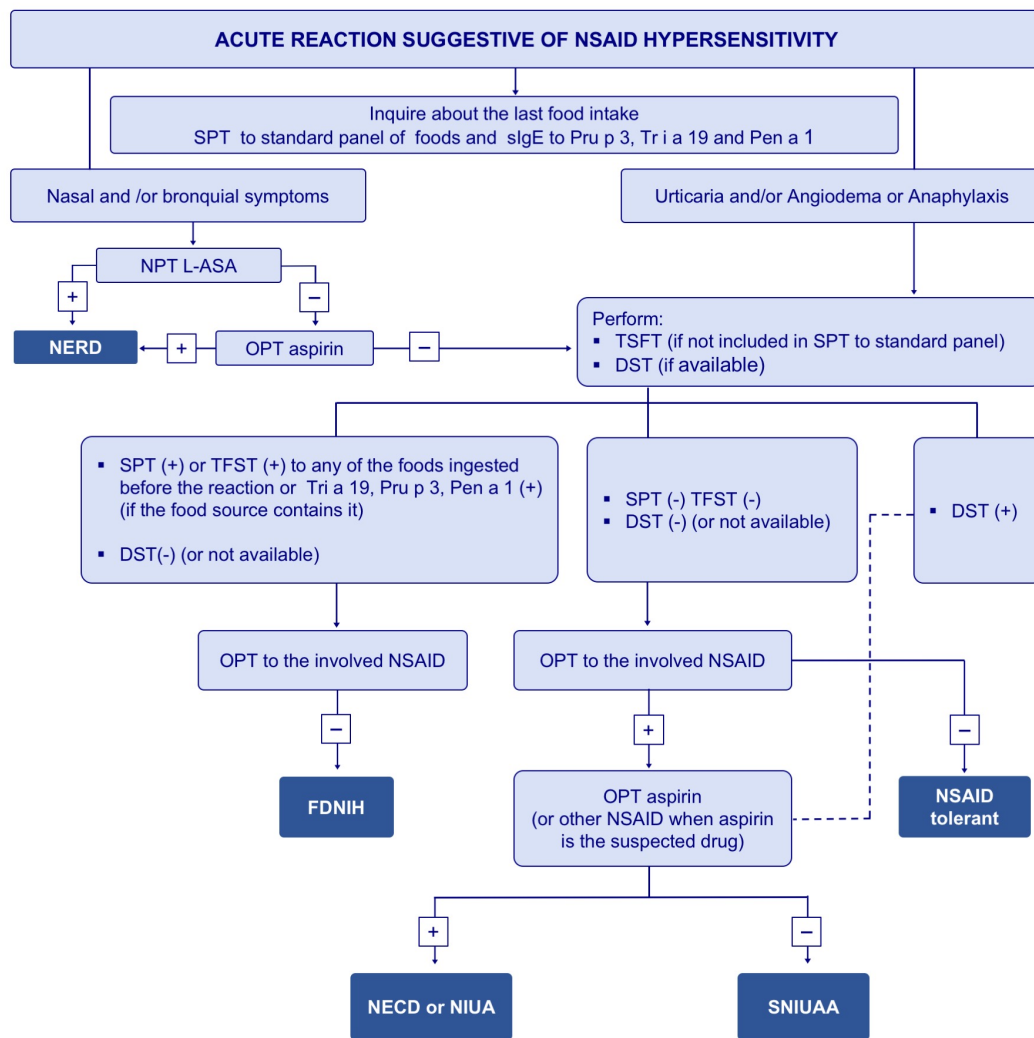


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