



Phenotypical characterization of children with hypersensitivity reactions to NSAIDs

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1 **Phenotypical characterization of children with hypersensitivity reactions to NSAIDs**

2

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21 **Abstract**

22 Cousin M, Chiriac A, Molinari N, Demoly P, Caimmi D.

23

24 **Phenotypical characterization of children with hypersensitivity reactions to NSAIDs**

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27 **Background.** Non-steroidal anti-inflammatory drugs (NSAIDs) are the main cause of drug-induced
28 hypersensitivity in children. Many classifications have been proposed, focusing on adults. So far, no
29 large study has deeply investigated a pediatric cohort. The aim of the present study was to describe
30 a population of NSAID hypersensitive patients reporting a reaction during their childhood, and to
31 verify if it is possible to classify pediatric patients, following the EAACI/ENDA classification.

32 **Methods.** We conducted a historical-prospective study including patients evaluated from 1996 to
33 2015 in the allergy unit of the Montpellier University Hospital. We included 635 patients. For each
34 patient, we recorded clinical manifestations and possible co-morbidities, and tried to identify
35 possible risk factors.

36 **Results.** NSAIDs hypersensitivity was diagnosed in 107 out of 635 patients (16.9%). In this group,
37 43 patients (40.2%) could not be classified following the ENDA recommendations. The main
38 discrepancies were on the patients' clinical manifestations and on their possible underlying diseases.
39 We identified, on a multivariate analysis, some risk factors for NSAID hypersensitivity: chronic
40 urticaria (OR 7.737, 3.375-18.296 95%CI), atopic status (OR 2.514, 1.504-4.364 95%CI) and
41 allergic rhino-conjunctivitis (OR 1.799, 1.138-2.837 95%CI). On the basis of our results, we are
42 proposing an adapted classification for NSAIDs hypersensitivity in children.

43 **Conclusions.** The current ENDA classification does not seem to be adapted for pediatric patients; a
44 modified version does. Our study could help allergists better understand the differences between
45 adults and children in developing hypersensitivity reactions to NSAIDs but further large-scale
46 prospective longitudinal analyses are required to validate this new classification.

47

48 **Key Words:** drug hypersensitivity, NSAIDs, children, classification, drug allergy.

49

50 The Authors have no conflict of interest to declare for the present paper.

51 **Introduction**

52 Non-steroidal anti-inflammatory drugs (NSAIDs) are widely used to treat fever and pain in
53 children. Nevertheless, they are currently considered as the first cause of drug-induced
54 hypersensitivity (HS) reactions in children (1, 2). Two different mechanisms are able to elicit HS
55 reactions: immunological mechanisms responsible for allergic HS reactions (such as IgE and T-cells
56 mediated reactions); and non-immunologic ones (mainly due to cyclooxygenases inhibition).
57 Several classifications have been proposed for NSAIDs HS, but no large study has so far tried to
58 classify NSAIDs HS focusing only on a pediatric population.

59 In 2001, Stevenson classified patients according to their clinical history but this classification did
60 not take into account the reactions recorded during drug provocation tests (DPTs) (3). Thereafter,
61 Quiralte proposed a classification with seven groups according to the patient's underlying disease
62 (4). The most recent NSAIDs HS classification highlighted five groups of patients, and has been
63 published by the European Network for Drug Allergy (ENDA) group, an EAACI drug allergy
64 Interest Group (5). This classification was based on the authors' expertise in hypersensitivity
65 reactions to NSAIDs. The publication does not differentiate between age groups, and it has to be
66 underlined that most of the expertise comes from adolescents and adults. Since its publication,
67 clinical observations and literature data (6) reported that some patients diagnosed with NSAIDs HS
68 could not be classified into the possible phenotypes described by the ENDA group (5). Moreover,
69 while the Widal's syndrome (or Samter's triad) is used as a reference phenotype for the first group
70 of the ENDA classification, "NSAID's-exacerbated respiratory disease", it is known that such a
71 syndrome has never been described before the age of 13 (7). In addition, a recent paper (1) reported
72 that the association of cutaneous and respiratory symptoms is frequently observed in children with
73 NSAIDs HS, which is a combination of different phenotypes proposed by the current classification,
74 but is not highlighted as a single group.

75 Considering the hypothesis that HS phenotypes may differ between the adult and pediatric
76 population, the aim of the present study was to describe a population of children with a diagnosis of

77 NSAIDs HS, and to try to classify them on the basis of the current ENDA recommendation. We also
78 tried to identify possible risk factors for NSAIDs HS in children, and to propose a pediatric version
79 of the ENDA classification.

80

81

82 **Methods**

83

84 ***Patients included***

85 We conducted a historical-prospective study including all patients evaluated at the allergy unit of
86 the University Hospital of Montpellier (France) for a clinical history of possible NSAIDs HS, which
87 occurred during the pediatric age, from September 1996 to July 2015, and who underwent an oral
88 DPT. Following the diagnostic work-up recommendations for NSAIDs HS (8), we classified
89 patients on the basis of the clinical reaction reported and the one recorded at the time of the DPT;
90 the different chemical classes of NSAIDs involved in their reaction; the presence of an underlying
91 chronic disease (asthma, chronic urticaria, chronic rhinosinusitis, atopy as defined by the presence
92 of at least one positive skin prick test to the common aeroallergens of Montpellier area); the delay
93 of reaction; and the suspected HS mechanism.

94 Clinical data were collected through the validated ENDA drug allergy questionnaire (9). DPTs were
95 performed under strict hospital surveillance at least four weeks after the last patient's HS reaction,
96 according to the unit's protocol (5, 10). Patients had not been taking any H1-antihistamines or other
97 drug possibly affecting the results of the test. Patients on β -blockers were asked to visit their
98 specialist to stop the drug 2 days prior to the test. Administration was single-blinded and performed
99 on the ward by a physician with full resuscitation back up. In case of a possible positive DPT,
100 another molecule would be tested to find a safe alternative for the patient, at least 4 to 6 weeks after
101 the previous DPT. All data were collected in the Drug Allergy and Hypersensitivity Database
102 (DAHD[®]) using FileMaker Pro 13 software.

103 We excluded all patients who had experienced severe life-threatening skin reactions (toxic
104 epidermal necrolysis and Stevens Johnson syndrome), drug-induced autoimmune diseases or severe
105 organ involvements (such as cytopenias, hepatitis, DRESS-Drug Reaction with Eosinophilia and
106 Systemic Symptoms), since DPTs are contra-indicated for such reactions. All patients refusing
107 DPTs were excluded as well. Written consent was obtained before the test after informing the
108 patients and the parents of children.

109

110 ***Clinical data***

111 For each patient, we looked for the following possible clinical entities, occurring both at the time of
112 the reaction and of the DPT: urticaria, angioedema (AO), maculopapular eruption, fixed drug
113 eruption, rhinitis, conjunctivitis, bronchospasm (defined by dyspnea associated with cough and/or
114 wheezing and/or a fall of 20% of the patient's basal FEV1 value), ENT-related dyspnea,
115 psychogenic dyspnea (diagnosis per exclusionem), gastrointestinal signs, anaphylaxis. Anaphylaxis
116 was defined as a rapid allergic response involving two different organs with or without associated
117 hypotension (11). Laryngeal angioedema associated dyspnea was considered as a muco-cutaneous
118 symptom.

119 We tested children with the culprit drug and, in case of a positive DPT, patients were tested, at least
120 4 weeks after the previous DPT, with a different NSAID, belonging to another chemical subgroup.
121 All together, 14 different NSAIDs have been tested, belonging to different chemical subgroups:
122 acetylsalicylic acid, celocoxib, diclofenac, etoricoxib, ibuprofen, ketoprofen, meloxicam,
123 metamizole, niflumic acid, nimesulide, piroxicam, trofecoxib, tiaprofenic acid.
124 Paracetamol/acetaminophen was included as well in the list of the 14 tested drugs.

125

126 ***Patients' classification***

127 In order to evaluate the accuracy of the ENDA classification (Table 1) in our pediatric cohort, we
128 tried to attribute each patient to the different ENDA groups, numbered from 1 to 5:

1. NSAIDs-exacerbated respiratory disease
2. NSAIDs-exacerbated cutaneous disease
3. NSAIDs-induced urticaria/angioedema
4. Single-NSAID-induced urticaria/angioedema or anaphylaxis
5. Single-NSAID-induced delayed reactions

Whenever a phenotype did not strictly correspond to one of the 5 groups, the patient was classified as “divergent” according to the following criteria:

- the patient was included in the group that seemed the closest to his phenotype;
- we used a letter to highlight for which feature of the group the patient did not properly fit in the ENDA classification: A – clinical manifestations; B – delay of the reaction; C – underlying disease; D – cross-reactivity (for example, an asthmatic patient who developed urticaria to several NSAIDs was classified as 3C);
- a patient divergent for more than one feature of the group was considered as “not possible to classify”.

Statistical analysis

Categorical data were expressed in frequencies and percent, continuous data in median and quartiles. To evaluate possible risk factors, we analyzed crude and adjusted odds ratio, with a 95% confidence interval. A multivariate analysis was conducted using a logistic regression model to determine independent risk factors of NSAIDs, in which we included all variables associated with a p value below 0.20 in the univariate analysis. Then, a stepwise procedure allowed obtaining the final multivariate model. We considered as statistically significant a p-value < 0.05.

Results

Patients’ characteristics, DPT and symptoms

635 patients fulfilled our inclusion criteria. In 107 out of 635 (16.9%) a reaction was recorded through the DPT, and a diagnosis of NSAIDs HS was reached. 62 out of 107 patients were female (57.9%). The characteristics of the age distribution of our patients are shown in Table 2.

In the group of the 107 diagnosed patients, 77 (72.0%) were atopic and 47 (43.9%) were sensitized to house dust mites. We are missing these data in 8 patients, that were therefore considered as non-atopic nor sensitized to mites. Also, 19 patients (17.8%) suffered from chronic urticaria, 45 (42.1%) reported symptoms of allergic rhino-conjunctivitis, and 37 (34.6%) were asthmatic. Two of the asthmatic patients, who were nevertheless adults at the time of their first DPT, presented with nasal polyposis as well. Other allergic diseases included atopic dermatitis (7 patients, 6.5%), food allergy (6 patients, 5.6%), chronic rhino-sinusitis (2 patients, 1.9%), other drug allergies (2 patients, 1.9%), and hymenoptera venom allergy (1 patient, 0.9%).

On a multivariate analysis, four risk factors were highlighted for NSAIDs HS: urticaria (adjusted OR 7.737, 3.375-18.296, 95%CI, p -value <0.001), atopy (adjusted OR 2.514, 1.504-4.364 95%CI, p -value <0.001), allergic rhino-conjunctivitis (adjusted OR 1.799, 1.138-2.837 95%CI, p -value 0.011), and the age at the first reaction (adjusted OR 1.083, 1.033-1.137 95%CI, p -value <0.001).

In the group of the 107 patients, we ran a total of 192 DPT: 46 patients (43.0%) only took one, and they did not come back to find a safe alternative, 44 (41.1%) underwent 2 DPT, 12 patients (11.2%) were tested for 3 different molecules, 3 (2.8%) for 4, and 2 patients (1.9%) came back 5 times to be tested.

Overall clinical symptoms presented by patients during their reported reaction and during DPT were: urticaria/angioedema (104 patients, 97.2%), bronchospasm (33 patients, 30.8%), conjunctivitis (31 patients, 29.0%), anaphylaxis (27 patients, 25.2%), ENT-related dyspnea (27 patients, 25.2%), maculopapular eruption (11 patients, 10.3%), rhinitis (8 patients, 7.5%), and gastro-intestinal symptoms (1 patient, 0.9%).

179

Classification of hypersensitive patients, according to the ENDA classification

181 Among the 107 patients with NSAIDs HS, 43 patients (40.2%) could not be completely classified in
182 the current ENDA classification and were divergent for one criterion, while 4 patients (3.7%) were
183 considered as “not possible to classify” (divergent for more than one criterion), as shown in Table 3.
184 Patients were divergent mainly for the feature A, “clinical manifestation” and C, “underlying
185 disease”. No patient was divergent for the feature B, “delay of reaction”. No patient strictly
186 corresponded to the group 1, “NSAIDs-exacerbated respiratory disease” of the ENDA classification
187 (Table 3).

188 Among the 22 patients belonging to the group 4, “single-NSAID-induced urticaria/angioedema or
189 anaphylaxis”, the main culprit drugs were paracetamol/acetaminophen (7 patients, 31.8% of the
190 group) and ibuprofene (7 patients, 31.8% of the group). All these patients had a negative DPT to at
191 least one other NSAID. The rest of the results are shown in Table 3.

192

193 *New possible pediatric classification*

194 On the basis of our results, we proposed a new classification in three groups, strictly derived from
195 the ENDA one. This classification remains focused on the pathophysiologic HS mechanism, but we
196 also included, as a feature, the impact of risk factors (urticarial, atopy, allergic rhino-conjunctivitis,
197 and age at first reaction). We excluded the presence of underlying diseases (which could occur later
198 in life), and modified the possible clinical manifestations (Table 4).

199 In this new classification, all our patients could be classified and no patient was divergent. We
200 included 91 patients (85.1%) in the group I, “non-allergic NSAIDs hypersensitivity”, 15 patients
201 (14.0%) in the group II, “single NSAID-induced urticarial/angioedema/anaphylaxis”, and 1 patient
202 (0.9%) in the group III, “single NSAID-induced delayed reactions”. The group I contains actually
203 groups 1 through 3 of the ENDA classification, and it has to be considered as a transitory group,
204 since patients may develop underlying chronic diseases throughout age. Even though a recent paper
205 did not highlight a correlation between NSAID-induced urticaria and evolution toward chronic
206 urticaria (12), these data refer to adult patients over a 12-years follow-up, and might differ from

207 what we might record in a strictly pediatric population. Therefore, so far, the evolution of the
208 immune system and the possible appearance of chronic diseases seem not to allow, in children, a
209 differentiation between the first 3 ENDA groups.

210

211

212 **Discussion**

213 Drug hypersensitivity is acquiring more and more importance in patients' everyday life. The
214 EAACI and the ENDA group in particular have proposed several protocols and tools to guide
215 allergists to perform a correct diagnosis and a complete allergy work-up in patients presenting with
216 a suspected hypersensitivity reaction to drugs. As for NSAIDs, a classification has been proposed in
217 2013, but it focused on adult populations. The fact that it is now clear that NSAIDs HS is a key
218 issue in the pediatric population as well, made it imperative to evaluate the appropriateness of such
219 a classification in this group of patients.

220 To our knowledge, we described the largest pediatric cohort with a diagnosis of NSAIDs
221 hypersensitivity. The first aspect highlighted by our results is that the ENDA classification did not
222 allow us to classify more than 40% of the patients, and it seems therefore clear that the current
223 recommendations are not suitable for the pediatric population.

224 According to a recent pediatric study by Cavkaytar et al. (13), who analyzed a cohort of 30 NSAIDs
225 hypersensitive patients, phenotypes are different in children and adults and pediatric subjects cannot
226 completely be classified in the latest classifications (5, 6). In the same study, 27% of patients were
227 diagnosed as NSAID hypersensitive and only one patient was classified in the group "NSAIDs-
228 exacerbated respiratory disease" of ENDA classification (13). Our results are similar to those
229 highlighted by Cavkaytar et al: in fact, the main problem we found in our cohort was related to the
230 first group proposed by ENDA, "NSAIDs-exacerbated respiratory disease", since none of our
231 patients could perfectly fit in this group. Indeed, this group was initially created for adults suffering
232 from late onset asthma, which is frequently associated with chronic rhino-sinusitis and nasal

233 polyposis and with a possible progression towards severe asthma (recurrent respiratory
234 exacerbations and corticosteroid-dependence) (14, 15).

235 Considering that NSAIDs HS, and drug HS in general, tends to persist over the years, we could
236 speculate that the evolution of children's immune system and the possible appearance of new and
237 persistent underlying diseases make it difficult to include patients in this group, even though the
238 same patients may belong to it once grown. Nevertheless, in a pediatric classification, it seems
239 inappropriate to classify children according to their underlying disease.

240 An interesting aspect of our results is that most of our patients (97.2%) reacted to NSAIDs
241 presenting urticaria and/or angioedema as a symptom. Therefore, mucocutaneous symptoms are not
242 specific during the pediatric age and not sufficient to differentiate and classify patients. Also, only
243 very few patients (1.9%) presented isolated bronchospasm as a symptom, and such a result is
244 confirmed by other authors (2, 16).

245 In the literature, physical exercise is often considered as a risk factor to develop an HS reaction to
246 NSAIDs; also, NSAIDs are known as a potential trigger for developing food allergy reactions (1).
247 However, recent NSAIDs HS classification did not include these risk factors. We did not find a
248 correlation between food allergy and NSAIDs HS, and we did not have patients who presented a
249 pediatric clinical history in which physical exercise was related to the appearance of HS symptoms
250 after NSAID intake (data not shown). In the literature, a significant association has been found
251 between house dust mites' sensitization and NASIDs hypersensitivity (14). In our study, atopy (but
252 not particularly house dust mites sensitization), urticaria, allergic rhino-conjunctivitis, and an early
253 reaction in life were found as significant risk factors for hypersensitivity reactions to NSAIDs.

254 Taking into account all of these considerations, we proposed a new classification for NSAIDs HS in
255 children, in which we included the presence of the previously mentioned risk factors, and we
256 neglected the presence of possible underlying chronic diseases. This classification could actually be
257 a helpful tool to understand the mechanisms leading to the HS reaction and to guide allergists in
258 their work-up.

259 A limitation of this study was that we didn't perform any skin test for the patients who presented
260 anaphylactic reaction or reaction to a single NSAID in their clinical history. Such data could help
261 proving the possible IgE mediated mechanism. Nevertheless, skin tests are not standardized nor
262 validated in clinical practice for NSAIDs and, more importantly, we preferred to use DPT as the
263 gold standard to reach a diagnose of hypersensitivity reaction. Also, we did not test many patients
264 with aspirin. This is due to the fact that such a drug is rarely prescribed in children, due to the risk
265 of Reye's syndrome, and, therefore, a clinical approach to NSAIDs hypersensitivity in children
266 cannot focus on such molecule, which, on the other hand, is often administered in the adult
267 population. Another possible limitation of the present study concerns the diagnosis of rhino-sinusitis
268 and nasal polyposis. Indeed, these diagnoses are mostly done in adult patients and require
269 endoscopic and/or imaging techniques. Therefore, we could not exclude an underestimation of these
270 diseases, even though, at least for nasal polyposis, such a diagnosis is rare during childhood and
271 generally related to other diseases.

272 In conclusion, during childhood every child is exposed at least once to a NSAID, and there are no
273 alternative, on a routine base, to treat fever and/or pain. An accurate classification of NSAIDs
274 hypersensitive patients could help better understand the pathology of these reactions and guide the
275 management of these patients since their early age. We believe that our study could help allergists
276 better understand the differences between adults and children in developing HS reactions to
277 NSAIDs and could indicate a possible way to modify the present classification.

278 **Bibliography**

- 279 1. Blanca-Lopez,N, Cornejo-García JA, Plaza-Serón MC et al. Hypersensitivity to nonsteroidal
280 anti-inflammatory drugs in children and adolescents: cross-Intolerance reactions. J Investig
281 Allergol Clin Immunol 2015: 25: 259-69.
- 282 2. Liew WK, Chiang WC, Goh AE. Paediatric anaphylaxis in a Singaporean children cohort:
283 changing food allergy triggers over time. Asia Pac Allergy 2013: 3: 29-34.
- 284 3. Stevenson DD, Sanchez-Borges M, Szczeklik A. Classification of allergic and
285 pseudoallergic reactions to drugs that inhibit cyclooxygenase enzymes. Ann Allergy Asthma
286 Immunol 2001: 87: 177-80.
- 287 4. Quiralte J, Blanco C, Delgado J et al. Challenge-based clinical patterns of 223 Spanish
288 patients with nonsteroidal anti-inflammatory-drug-induced-reactions. J Investig Allergol
289 Clin Immunol 2007: 17: 182-8.
- 290 5. Kowalski ML, Asero R, Bavbek S et al. Classification and practical approach to the
291 diagnosis and management of hypersensitivity to nonsteroidal anti-inflammatory drugs.
292 Allergy 2013: 68: 1219-32.
- 293 6. Caimmi S, Caimmi D, Bousquet PJ, Demoly P. How can we better classify NSAID
294 hypersensitivity reactions? – Validation from a large database. Int Arch Allergy Immunol
295 2012: 159: 306-12.
- 296 7. Ameratunga R, Randall N, Dalziel S, Anderson BJ. Samter's triad in childhood: a warning
297 for those prescribing NSAIDs. Pediatr Anesth 2013: 23: 757-9.
- 298 8. Kowalski, M. L. and J. S. Makowska. Seven steps to the diagnosis of NSAIDs
299 hypersensitivity: how to apply a new classification in real practice? Allergy Asthma
300 Immunol Res 2015: 7: 312-20.
- 301 9. Demoly P, Kropf R, Bircher A, Pichler WJ. Drug hypersensitivity: questionnaire. Allergy
302 1999: 54: 999-1003.
- 303 10. Messaad D, Sahla H, Benahmed S, Godard P, Bousquet J, Demoly P. Drug provocation tests

- in patients with a history suggesting an immediate drug hypersensitivity reaction. *Ann Intern Med* 2004; 140: 1001-6.
11. Sampson HA, Muñoz-Furlong A, Campbell RL. Second symposium on the definition and management of anaphylaxis: summary report-Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. *J Allergy Clin Immunol* 2006; 117: 391-7.
12. Doña I, Blanca-López N, Torres MJ et al. NSAID-induced urticaria/angioedema does not evolve into chronic urticaria: a 12-year follow-up study. *Allergy* 2014; 69: 438-44.
13. Cavkaytar O, Arik Yilmaz E, Karaatmaca et al. Different Phenotypes of Non-Steroidal Anti-Inflammatory Drug Hypersensitivity during Childhood. *Int Arch Allergy Immunol* 2015; 167: 211-21.
14. Ayuso P, Blanca-López N, Doña I et al. Advanced phenotyping in hypersensitivity drug reactions to NSAIDs. *Clin Exp Allergy* 2013; 43: 1097-109.
15. Berges-Gimeno MP, Simon RA, Stevenson DD. The natural history and clinical characteristics of aspirin-exacerbated respiratory disease. *Ann Allergy Asthma Immunol* 2002; 89: 474-8.
16. Zambonino MA, Torres MJ, Muñoz C et al. Drug provocation tests in the diagnosis of hypersensitivity reactions to non-steroidal anti-inflammatory drugs in children. *Pediatr Allergy Immunol* 2013; 24: 151-9.