G. Colombo, M.R. Yacoub, S.E. Burastero, E. Garattini, S. Girlanda, N. Saporiti, F. Salvo, M.G. Sabbadini

Multiple drug hypersensivity: insight into the underlying mechanism and correlation with autoimmune diseases

Allergy and Immunology Department, IRCCS San Raffaele Hospital, Milan, Italy

Key words

Autoimmune diseases, chronic idiopatic urticaria, diagnosis, management, multiple drug hypersensitivity

Summary

Background: *Subjects with drug hypersensitivity are sometimes simultaneously reactive to several drugs. This nosological entity is defined as multiple drug hypersensivity (MDH). Urticaria and angioedema are the commonest clinical manifestations of hypersensitivity drug reactions (HDR). These clinical signs are also pathognomonic of chronic idiopathic urticaria (CIU), whose pathogenetic mechanisms are still largely unknown. The diagnostic algorithm of CIU includes autologous serum skin test (ASST) and autologous plasma skin test (APST), which demonstrated a high positive and negative predictive value, in multiple nonsteroidal anti-inflammatory drugs (NSAIDs) intolerance.* ***Objectiv****e: to explore the underlying mechanism of MDH and to assess the correlation between such tests and autoimmune diseases (AD).* ***Methods:*** *Twenty eight subjects with MDH referred to our Allergy/Immunology Unit were enrolled from May 2006 to May 2007. Eight healthy subjects served as controls. In addition to common diagnostic tools used in the diagnostic algorithm of MDH, enrolled subjects also underwent ASST and APST.* ***Results:*** *Patients were predominantly female (23 female vs 5 male; mean age 52.2 years). In 61% of cases MDH was associated with either CIU or AD. NSAIDs and antibiotics were the major causes of HDR, both implied in 54% of subjects. The proportions of MDH-subjects with positive ASST and APST were 46.4% and 28.6%, respectively. All patients with MDH+AD+CIU (4/4) presented a positive ASST.* ***Conclusions:*** *In patients with MDH, ASST proved to be frequently positive, as previously described for multiple NSAIDs intolerance. In ASST-positive subjects, the activity of several drugs appears to add up FceRI-specific autoantibodies in the induction of the release of allergic mediators.*

Introduction

Subjects who experience an adverse reaction to a single drug sometimes display similar reactions to several others. Non steroidal anti-inflammatory drugs (NSAIDs) and antibiotics are those more commonly implicated. This nosological entity is defined as multiple drug hypersensitivity (MDH). In MDH the pathogenetic mechanism involved in degranulation of mastocytes and basophils does not depend on drugs molecular structures, which often are widely different, but on poorly characterized host's intrinsic factors (1). Urticaria and angioedema are among the commonest clinical manifestations of adverse reaction to drugs. These clinical signs are also pathognomonic of another clinical entity, namely chronic idiopathic urticaria (CIU), whose pathogenesis remains unknown.

Autologous serum skin test (ASST) is a recognized tool in the diagnostic pathway of chronic urticaria (2). This test identifies subjects with serum factors which cause histamine-release from mastocytes, an event clinically associated with urticaria. An additional and recently proposed diagnostic tool for CIU is the autologous plasma

skin test (APST) (3). This test allows the identification of subjects with a high level of a factor (F1+2), generated following thrombin formation starting from prothrombin. It has been demonstrated that thrombin may induce rat mast cell degranulation and has consequently a histamine-releasing activity (4).

The available tools for the diagnosis of drug allergy are presently limited to clinical history, prick test, specific IgE dosage and basophils activation test (BAT). However specific IgE dosage is available only for a few drugs, and BAT is offered only in a few specialized centers. Moreover sensitivity of specific IgE dosage and BAT is affected by the latency time since the hypersensitivity reaction occurred. The gold standard for the management of patients with MDH consists in tolerance tests with alternative drugs or provocative challenge with the incriminated drug, if irreplaceable.

The aim of our study is to evaluate potential additional value of ASST and APST in the diagnostic algorithm of MDH, and to assess the correlation between MDH, CIU and autoimmune diseases (AD).

Materials and methods

Twenty-eight consecutive adult subjects (male/female: 5/28; mean age: 53.4 years range: 18-80 years) suffering of systemic MDH were enrolled at our Allergy and Immunology Unit from May 2006 to May 2007. This group represents 23.3% (28/120) of subjects who referred to our Unit in the same period with a HDR clinical history, to undergo a tol-

Table 1 - Main characteristics of the study population

Patients	Sex	Age	AD	CIU	Symptoms	ASST positive	APST positive
1	F	80	NO	NO	U/A	NO	NO
2	F	48	NO	NO	U	NO	NO
3	M	22	NO	NO	U/A	YES	NO
4	F	65	NO	NO	U/A	YES	NO
5	M	71	NO	NO	U	NO	NO
6	F	43	NO	NO	A/AS	NO	NO
7	F	59	NO	NO	U/A	YES	YES
8	M	38	NO	NO	U	YES	YES
9	F	63	NO	NO	U/A	NO	NO
10	F	18	NO	NO	U	NO	NO
11	F	36	NO	NO	U/A	NO	NO
12	F	42	HT	NO	U/A	NO	YES
13	F	68	Sjogren	NO	U/A	NO	NO
14	F	44	HT	NO	A/AS	NO	NO
15	F	57	HT	NO	U/A	NO	NO
16	F	68	HT	NO	U/A	YES	YES
17	F	61	HT	NO	U/A/AS	NO	NO
18	F	57	HT	NO	U/AS	NO	NO
19	F	45	HT	NO	U/A	YES	NO
20	F	27	HT	YES	U	YES	NO
21	F	40	NO	YES	U	NO	NO
22	M	53	NO	YES	U	YES	YES
23	F	58	NO	YES	U/A	YES	YES
24	F	63	NO	YES	U/A	NO	NO
25	F	49	HT	YES	U/A	YES	NO
26	M	58	HT	YES	U/A	YES	YES
27	F	59	HT	YES	U/AS	YES	NO
28	F	69	UCTD	YES	A/AS	YES	YES

AD: autoimmune diseases; CIU: chronic idiopathic urticaria; AS: anaphylactic shock; ASST: autologous serum skin test; APST: autologous plasma skin test, UCTD: undifferentiated connective tissue disease

erance challenge with an alternative drug. All subjects underwent a screening for AD (thyroid autoantibodies and ANA dosage). An accurate anamnesis regarding allergic diseases was acquired and the diagnosis of MDH was made when patients reported hypersensitivity reactions to two or more drugs with different molecular structure. A group of 8 subjects with only AD, a group of 8 subjects with only CIU, and a group of 8 healthy subjects (without MDH nor AD nor CIU), were also included in the study. Antihistamines and steroidal treatment were withdrawn at least 5 days prior to skin tests. Other exclusion criteria were: food allergy or additive intolerance, history of neoplasia (solid or hematologic), physical urticaria and infections. According to the concomitant occurrence of AD and/or CIU the MDH included subjects were classified into two groups: group A=patients with isolated MDH; group B=patients with MDH and/or AD and/or CIU. The diagnosis of CIU was made in subjects with continuous or recurrent urticaria since more than 6 weeks, after having excluded other causes of CU (5).

All patients gave written informed consent. Blood was drawn by venipuncture in Vacutainer® vials with no additive (for serum) and in vials containing Na citrate as an anti-coagulant reagent (for plasma), Serum and plasma were separated by centrifugation at 2000 rpm for 10 minutes. All subjects underwent ASST and APST. To this aim, aliquots (50 µl) of autologous serum, autologous plasma, and 0.9% sterile saline were separately injected into the volar aspect of the forearm. Skin prick test with histamine 10 mg/ml was carried out as positive control. Areas known to have been involved in spontaneous wheals in the last 24 h were avoided. Wheals and flair responses were measured at 20 minutes. The test was considered positive in case of a wheal response > 1.5 mm in ASST and > 3 mm in APST, compared with negative control (sterile saline solution) developed, as previously described (6, 7).

Statistic

Inter-group comparisons of ASST and APST results in patients with isolated MDH and in those with MDH and/or AD and/or CIU, were performed with the exact Fisher's test for categorical data. A p value < 0.05 was considered statistically significant.

Results

Systemic MDH was diagnosed in 28/120 (23.3%) subjects who were referred to our Allergy and Immunology Unit from May 2006 to May 2007 with a clinical history of HDR. Isolated MDH (group A) was diagnosed in 11/28 patients (39,2%), MDH associated with AD and/or CIU in 17/28 (60.8%). In particular 9/28 patients (32,1%) had MDH associated with AD, 4/28 patients (14,28%) MDH associated with CIU and 4/28 patients (14,28%) MDH associated with both conditions. Hashimoto's thyroiditis resulted the most frequent AD associated with MDH, observed in 11/28 (39.3%).

In our study, NSAIDs and antibiotics were the more involved drugs in MDH. In particular, 26/28 subjects (92.8%) had allergic reactions after assumption of NSAIDs, 17/28 (46.4 %) had antibiotics allergy and 14/28 patients (50%) were allergic to both classes of drugs (NSAIDs and antibiotics). HDR to antibiotics and NSAIDs was found in 7/11 (63.6%) in group A and in 7/17 (41.2%) in group B (p= 0.4401,n.s.). Detailed information on drugs implied in adverse reactions are reported in table 2. Thirteen out of twenty-eight patients (40.6%) scored positive on the ASST, 4/11 (36.3%) in group A and 9/17 (52.9%) in group B (p=0.4601, n.s.). Eight out of twenty-eight subjects (28.5%) scored positive on the APST, 2/11 (18.1%) in group A and 6/17 (35.2%) in group B (p=0.4188). ASST resulted positive in 1/8 subject (12.5%) in the group with isolated AD, in 1/8 subject (12.5%) with isolated CIU and in 4/11 subjects (36.4%) with isolated MDH. All subjects with MDH+AD+CIU had a positive ASST (p 0.05 versus group with isolated MDH). Both ASST and APST were negative in healthy controls.

Discussion

Our study was based on a previous observation on patients with previous systemic HDR, hospitalized at our Unit to perform a tolerance challenge with an alternative drug (data not published). Twenty out of 121 patients had an associated AD, in particular Hashimoto's thyroiditis, Graves disease, Sjogren syndrome, systemic lupus erythematosus or rheumatoid arthritis. In the AD subgroup of patients, 11 (55%) had a significant clinical history of HDR, mainly represented by urticaria and angioedema, to several drugs with different molecular structures. This nosological entity is defined as multiple drug hypersensivity (MDH). The pathogenetic mechanism of MDH involves the degranulation of mastocytes and basophils induced by several drugs with different molecular structure. The commonest clinical manifestations of MDH are urticaria and/or angioedema, but also anaphylactic shock might occur. MDH prevalence

is still under investigation even if data from the literature show that 5% of hospitalized patients present HDR (8), and the patients with AD are more often implied (9-11).

In MDH subjects, mastocytes and basophils degranulation might be induced by serum and or plasma host factors rather than by specific drug molecules. In this scenery the

Table 2 - Category and molecules of drugs implied in hypersensitivity reactions

Groups	Patients	Drugs implied in hypersensitivity
MDH	1	NSAIDs (acetylsalycilic acid, pyrazolic compounds); antibiotic (amoxicillin)
	2	NSAIDs (acetylsalycilic acid, nimesulide); antibiotic (clarytromycin)
	3	NSAIDs (acetylsalycilic acid); cetirizine
	4	NSAIDs (acetylsalycilic acid, nimesulide); antibiotic (miomycin)
	5	NSAIDs (acetylsalycilic acid, nimesulide); antibiotic (ciprofloxacin)
	6	NSAIDs (acetylsalycilic acid, ibuprofen); antibiotic (cotrimoxazole)
	7	NSAIDs (acetylsalycilic acid, naproxen); antibiotic (roxithromycin,ceftazidime)
	8	NSAIDs (nimesulide); antibiotics (clarithromycin, amoxicillin)
	9	NSAIDs (ketoprofen, nimesulide)
	10	NSAIDs (acetaminophen, nimesulide, acetylsalycilic acid)
	11	Antibiotics (roxithromycin, clindamycin, cefixime)
MDH + CIU and/or AD	12	NSAIDs (acetylsalycilic acid, acetaminophen), codeine
	13	NSAIDs (acetylsalycilic acid), antibiotics (neomycin, sulfathiazole)
	14	NSAIDs (acetylsalycilic acid, nimesulide), penicillin
	15	NSAIDs (diclofenac, nimesulide); antiarrhythmic
	16	Antibiotics (clarytromycin, vancomycin, tinidazole), ranitidine, amiodarone
	17	Antibiotics (amoxicilline, rifamycin, isoniazid, sulfamethoxazole), antitetanic prophylaxis
	18	NSAIDs (diclofenac), antibiotics (amoxicillin, clarithromycin)
	19	NSAIDs (acetylsalycilic acid, acetaminophen, nimesulide)
	20	NSAIDs (nimesulide), sulfonamide
	21	NSAIDs (acetylsalycilic acid, naproxen), antibiotic (amoxicillin)
	22	NSAIDs (acetylsalycilic acid), antibiotic (clarithromycin)
	23	NSAIDs (acetylsalycilic acid, nimesulide), antibiotics (amoxicillin, gentamycin)
	24	NSAIDs (acetylsalycilic acid, nimesulide)
	25	NSAIDs (acetylsalycilic acid, nimesulide), chlorphenamine
	26	NSAIDs (acetylsalycilic acid, ketoprofen)
	27	NSAIDs (acetylsalycilic acid, nimesulide)
	28	Antibiotics (amoxicillin, norfloxacin, nitrofurantoin)

MDH: multiple drug hypersensitivity; AD: autoimmune disease; CIU: chronic idiopathic urticaria; NSAIDs: non steroidal antiinflammatory drugs.

Table 3 - Results of ASST and APST in the different groups of subjects

Patients	M/F	Mean Age (years)	NSAIDs' Allergy	Antibiotics' Allergy	Positive ASST	Positive APST
MDH	3/8	49,3	10/11 (90.9%)	8/11 (72.7%)	4/11 (36.3%)	2/11 (18.1%)
MDH + AUT	0/9	56,1	9/9 (100%)	5/9 (55.5%)	3/9 (33.3%)	2/9 (22.2%)
MDH + CIU	1/3	53,5	3/4 (75%)	3/4 (75%)	2/4 (50%)	2/4 (50%)
MDH + CIU + AUT	1/3	58,8	4/4 (100%)	1/4 (25%)	4/4 (100%)	2/4 (50%)
Total	5/23	53,4	26/28 (92.8%)	17/28 (60.7%)	13/28 (46.4%)	8/28 (28.5%)

drug could act as a trigger in a complex chain reaction that involves mastocytes and basophils, leading to "allergic" manifestations. ASST and APST are already included in the algorithm of CIU, and have demonstrated a high positive and negative predictive value in multiple NSAIDs intolerance (12). The main objective of our work was the clarification of the underlying mechanism of MDH and the correlation between the result of ASST and APST and AD. We therefore performed ASST and APST in all subjects with a clinical history of systemic MDH. The tests were also performed in a subgroup of 8 subjects with isolated CIU, others 8 subjects with isolated AD and in 8 healthy subjects.

The main findings of our preliminary study are that: (1) our study population was selected in a group of 120 subjects with a single (92/120, 76.7%) and a multiple (28/120, 23.3%) drug hypersensitivity. MDH is therefore not so rare, as previously described (13, 14). Twelve MDH subjects (12/28, 42%) presented a hypersensitivity reaction either to NSAIDs or to antibiotics. No correlation was found between the positivity of APST and ASST the drug class or the severity of the reaction, in agreement with a previous report on APST (4, 15). As a matter of fact, only one patient with a clinical history of drug-induced anaphylactic shock had a weak positivity to ASST; (2) MDH, CIU and AD were frequently associated (17/28, 60.7%), suggesting that MDH might have an autoimmune/autoreactive background. In fact, prevalence of thyroid-targeted autoimmune conditions in the general population is strikingly lower, namely around 0.1-5% and 0.1-0.2% in Hashimoto thyroiditis and Graves disease, respectively (3, 16). Prevalence of positive ASST among subjects with MDH is relevant (13/28, 46.4%), as previously described by Asero et al. (17). We can therefore assume that in patients with MDH, histamine release could be mediated by a serum factor, as described for autoimmune urticaria; (4) Prevalence of positive ASST among subjects with MDH+AD+CIU is relevant (4/4), and higher than in subjects with isolated MDH (4/11, 36.4%, p: 0.05); (5) prevalence of positive APST among subjects with MDH is lower comparing to that of positive ASST (8/28, 28.5%), and only 1 subject shows a positive APST and a negative ASST (in group B: MDA+AD). ASST and APST positivity was lower than that reported by Asero and collaborators. This discrepancy could be partly explained by the different population selection criteria: Asero performed these tests in patients with different grade of hypersensitivity drug severity, whereas our study population included only subjects with hypersensitivity reactions serious enough to justify an hospitalization. This could have selected a particular population with different intrinsic factors, that could account for an autoreactive background. Taken together all these findings provide a further insight in the mechanism of MDH, suggesting that this condition may be associated to an autoimmune/autoreactive phenotype. We speculate that in MDH subjects several drugs add up their activity to that exerted by FceRI-specific autoantibodies, inducing a non-specific release of allergic mediators. In this context the effectiveness of a prophylactic antihistaminic therapy, taken before the use of any drug, may prevent further HDR. The appropriateness of a similar strategy in patients with MDH needs to be verified. Our preliminary data suggest that patients with AD and positive-ASST had an increased risk to develop HDR. In this perspective, autoimmune antibodies assessment and ASST might be included in the flowchart of patients with MDH; Further studies on larger population are required to enforce our findings.

Conclusion

Our preliminary data indicate that ASST is often positive in MDH patients and that MDH seems to be associated with autoimmune thyroiditis. These findings provide a further insight in the mechanism of MDH, and suggest that MDH might have an autoimmune/autoreactive background.

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