



Multiple drug hypersensitivity syndrome

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Purpose of review

The multiple drug hypersensitivity syndrome (MDH) is a distinct clinical entity, different from cross-reactivity and flare-up reactions. Following its initial description in 1989 by Sullivan *et al.*, several authors have addressed the issues surrounding this peculiar form of drug hypersensitivity. Whether this syndrome is single or can be further classified in several entities is still a matter of debate.

Recent findings

Case reports, case series or studies involving large populations on MDH are few. The use of this term in the literature is heterogeneous, and the definitions variable. Given the major advances in the study of drug hypersensitivities in general, and ongoing research regarding severe cutaneous adverse reactions in particular, careful study of the subgroup of patients with demonstrated immunological basis of MDH has enabled the generation of possible pathogenetic hypotheses. Together with the studies (despite their limitations) to estimate the prevalence of this syndrome in adult and paediatric patients these emerging data need confirmation through larger studies with well defined populations.

Summary

Bringing together the experience of groups involved in the field of drug allergy should help to move knowledge regarding this peculiar form of drug hypersensitivity forward.

Keywords

multiple drug hypersensitivity syndrome, neosensitization, severe cutaneous adverse reaction

INTRODUCTION

Drug hypersensitivity reactions (DHR) affect more than 7% of the general population and therefore represent an important public health problem [1]. Both underdiagnosis (due to underreporting [1,2]) and overdiagnosis (due to the overuse of the term 'allergy' [1,3]) are potential problems.

There are certain false assumptions regarding DHR, and misclassification based on the DHR history alone may have consequences on individual treatment choices. Patients frequently report 'multiple drug allergies' (most of which are not validated) leading to a negative impact on the quality of medical care [4].

About one-third of patients consulting in a drug allergy unit report 'multiple drug allergies' [5^{••},6[•]].

NOMENCLATURE: MULTIPLE DRUG ALLERGY/HYPERSENSITIVITY SYNDROME VERSUS MULTIPLE DRUG INTOLERANCE SYNDROME

First described in 1989 by Sullivan *et al.* [7] as drug allergies to two or more chemically different drugs (which were mainly antibiotics), the multiple drug allergy syndrome is a peculiar clinical entity,

different from cross reactivity (due to structural similarities, common metabolic pathways or pharmacologic mechanisms) and flare-up reactions (accounting for the exacerbation of an existing drug hypersensitivity by the early switch of therapy to another drug) [8].

In light of the established nomenclature in allergy [9], as well as of the current knowledge regarding drug hypersensitivity, the term multiple drug hypersensitivity syndrome (MDH) would probably be more appropriate in order to clearly define this entity. MDH should be reserved for cases in which the diagnosis of DHR has been made by appropriate drug allergy work-up, and should not be used as an umbrella concept.

Not surprisingly, MDH is barely mentioned in most guidelines tackling drug hypersensitivity. Even though several authors have addressed the issue of

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KEY POINTS

- The term 'multiple drug hypersensitivity syndrome' should be reserved for cases in which the diagnosis of drug hypersensitivity has been made by appropriate drug allergy work-up.
- Both sequential and simultaneous sensitizations to different drug classes may occur, and coexistence of immediate and delayed-type drug hypersensitivities in the same patient has been described.
- Practitioners should be aware of this peculiar form of drug hypersensitivity, and that for at least one subgroup of patients, circumstances of onset (such as a history of severe cutaneous adverse reaction, especially DRESS) seem to be a risk factor.

MDH, either with respect to its mechanisms or frequency, the reports of MDH are rather scarce and were previously mostly based upon positive clinical history alone. Its pathomechanism is still unclear, bringing about confusion concerning its definition. Hence, one of the obvious weaknesses of the review of articles tackling MDH lies in the heterogeneous use of this term in the literature, defining different populations that are actually not MDH (i.e. nonsteroidal anti-inflammatory drug cross-intolerant patients) as well as the absence of clear insight into the underlying pathophysiologic mechanisms.

The multiple drug intolerance syndrome (MDIS) [10] holds a peculiar place in a review covering the topic of MDH, precisely for the above-mentioned reasons. Certain patients, reporting various adverse drug reactions to three or more chemically, pharmacologically and immunogenically unrelated drugs, taken independently, and who display certain negative allergological tests (skin tests and specific IgE measurements to the putative drugs), are considered by some authors to suffer from MDIS. These patients typically undergo challenge tests (with or without premedication) with alternative drugs, avoiding those belonging to the same families that had provoked the initial symptoms or sharing the same action. A marked psychosomatic component may play a role in MDIS, especially in female patients, who represent more than three-quarters of this group of patients.

In a large population-based study [11] carried out in the United States, analysing electronic medical record data from over 2 million health plan members, the frequency of MDIS was estimated at 2.1%.

Whereas the diagnosis of MDH is established following positive drug allergy work-up, in MDIS,

it is rather the therapeutic approach that is favoured, by medication avoidance and challenge test with alternative drugs. Therefore, these two entities are distinct and MDIS should not be mistaken for MDH. MDIS is obviously not under the scope of our review.

PHENOTYPES OF MDH AND THEIR EPIDEMIOLOGY

In the early studies addressing the prevalence of MDH, its real estimation was hampered by the lack of a thorough allergy work-up. Hence, self-reported MDH, as opposed to documented MDH, was assessed in penicillin-allergic patients [12,13] or in specific populations, including HIV positive [14] and lupus patients [15].

More recent reports [16,17,18] provided in-vivo (skin tests) and/or in-vitro (lymphocyte transformation test – LTT) proof of MDH in a limited number of patients. Based on a definite diagnosis, certain phenotypes seemed to arise.

Pichler *et al.* [18] suggested two subtypes of MDH: one which develops against different drugs given simultaneously, and a second in which the sensitisations develop sequentially, sometimes years apart. The same group [8] estimated that in their experience, most patients have had rather severe reactions (namely bullous exanthema, severe long-lasting and generalized maculopapular exanthema and drug reaction with eosinophilia and systemic symptoms, DRESS) to at least one drug, and that multiple T-cell reactions with distinct clinical pictures have developed, but not IgE and T-cell mediated reactions together. This observation was supported by the findings of Gaig *et al.* [19], who reported five patients with evidence of neosensitization to chemically or antigenically unrelated drugs administered during anticonvulsant-related DRESS. More recently, other authors [5[¶],6[¶],20[¶]] have found both types of DHR in a limited number of patients.

In documented DHR, the prevalence of MDH varies greatly, presumably according to the studied population. The initial report by Sullivan *et al.* [7] estimated that 1% of 437 penicillin-allergic patients reacted to a nonbetalactam antibiotic. This observation was restricted to immediate type reactions to penicillins. In two recent retrospective reports involving large series of patients, each covering more than a decade of drug allergy work-up and comprising various clinical presentations of DHR, MDH was diagnosed in 0.6% [0.3%, if severe cutaneous adverse drug reactions (SCAR) were excluded] of 1925 [20[¶]] and 0.56% (26) of 4612 [6[¶]] consecutive patients, respectively. Interestingly, although the prevalence of proven DHR in children

is lower than in adults, Atanaskovic *et al.* [5^{••}] reported MDH in seven out of 279 children (2.5%) evaluated for suspected DHR, over a 5-year period. In this series, one single patient had a history of SCAR, namely Stevens Johnson syndrome (SJS).

In studies addressing only delayed-type DHR, even though the number of MDH patients is still low per se, the percentage seems to be higher, ranging from 10 [16] to 50% [21]. In this latter report, out of 12 patients with delayed-type DHR to iodinated radiocontrast media (proven by means of skin tests, lymphocyte activation and transformation tests and histological findings), six patients displayed various delayed-type DHR to different drugs.

In the largest prospective multicenter study [22^{••}] to date (134 patients), assessing the value and safety of skin tests, and particularly patch tests for three types of SCAR, namely, DRESS, acute generalized exanthematous pustulosis (AGEP) and SJS/TEN, the multiple drug reactivity (MDR), as defined by positive skin testing to multiple drugs administered simultaneously during the DHR, was found in 18% of the positive DRESS cases. None of these 13 patients reported a history of DHR, prior to the occurrence of DRESS, suggesting the hypothesis of concomitant sensitisation. In AGEP and SJS/TEN, MDR to different drug classes was less frequent, and occurred in three out of 45 (6.6%) and one out of 17 (5.8%) cases, respectively.

The most relevant studies regarding demonstrated MDH are summarized in Table 1.

RISK FACTORS FOR MDH

Not surprisingly, studies aiming to identify risk factors for MDH are closely related to the advances in knowledge about DHR. Early studies must be interpreted with caution, as self-reported multiple DHR, rather than documented MDH, were studied.

Following the initial reports by Smith *et al.* [23] and Sullivan *et al.* [7], regarding the higher self-reported DHR and the documented MDH, respectively, in penicillin-allergic patients, Khoury and Warrington [12] conducted a matched-control retrospective study in 44 patients allergic to penicillin. The authors concluded that no evidence for a significant increase in self-reported DHR frequency to non- β -lactam antimicrobials was found in their series.

Studies conducted in the nineties in patients infected with HIV [14] or suffering from systemic lupus erythematosus [15] suggest that reported multiple antibiotic allergy is more common in these populations.

More recent studies place SCAR, and particularly DRESS, at high risk of inducing multiple

sensitizations and thus they increase the understanding of, at least a part of the spectrum of MDH pathways [18,22^{••},24^{••}].

PATHOGENESIS OF MDH

In 2001, Hari *et al.* [17] investigated the T-cell activation and drug specificity in a series of 22 patients with histories of drug-induced exanthemas, of different severity. Two of them, with a history of bullous exanthema, displayed T-cell proliferation (as assessed by both positive LTT and patch tests) to two different antibiotic compounds, given simultaneously. The authors hypothesized that this reactivity might indeed reflect a true sensitisation to multiple drugs.

Later, the same group [18] described a series of patients matching the definition of MDH and proposed the two subtypes of sensitization, concomitant and sequential. Their observations were confirmed by other authors [19,21].

By focusing on a subgroup of MDH patients, namely those with a proven immunological basis (the majority of which presented with severe forms of drug allergy, including DRESS), Daubner *et al.* [24^{••}] investigated Tregs, which are plausible candidates to search for the inadequate down-regulation in SCAR. They found an imbalance of the immune system caused by excessive activation of effector T-cells or an inadequately low function or number of Treg cells. In this regard, but outside the context of MDH, Takahashi *et al.* [25] reported a significant expansion of functional Treg cells during the acute phase in DRESS patients, which was followed by deficient Treg cell function after recovery. To address this hypothesis in MDH patients, Daubner *et al.* [24^{••}] conducted a case-control study, by comparing the activation of different T-cell subpopulations in MDH patients, monoallergic patients and healthy controls. They found that (at least) for a subgroup of MDH patients, the main difference between MDH and monoallergic patients was not a deficiency in Treg function or number, but the fact that the drug-reactive T-cells belonged to an *in vivo* previously undescribed preactivated cell fraction (namely CD4⁺ CD25^{dim}), whereas those from monoallergic patients resided in the resting CD4⁺ CD25^{neg} T-cell fraction. Contrary to the observation made by Takahashi *et al.*, Treg function was preserved in all drug-allergic patients in the clinical remission phase as well as later on (but was not studied in the acute phase).

In this subgroup of patients, with T-cell mediated MDH, whether the sensitizations occur simultaneously or years apart, several aspects are worth mentioning:

Table 1. Studies providing evidence of multiple drug hypersensitivity syndrome patients

Author/year of publication	Clinical histories of tested patients	Number of tested patients	Studied population	Type of studied population	Patients with confirmed MDH [number (%)]	Drug allergy work-up	Comments	Drugs involved (from the most to the least prevalent ones)
Atanaskovic <i>et al.</i> , 2012 [5 [■]]	Immediate and delayed-type DHR	279	Patients consulting for a suspicion of DHR	Children ^a	7 (2.5%)	ST, DPT	The largest study regarding proven MDH in children	Antibiotics, antiepileptics, NSAIDs, corticosteroids, general anesthetics
Mean age 8.7 (SD 3.79); range 2–14 years								
Barbaud <i>et al.</i> , 2013 [22 [■]]	Delayed-type DHR	134	Patients consulting for a suspicion of severe DHR	Children and adults ^a	17 (12.6%)	ST	The largest multicentre prospective study addressing the value and safety of patch tests in 3 types of SCARs: DRESS, AGEF, SJS/TEN	Antibiotics, proton pump inhibitors, antiepileptics, diuretics, antivirals, anticoagulants
Mean age 51.7 years; range 3–94 years								
Chiriac <i>et al.</i> , 2012 [6 [■]]	Immediate and delayed-type DHR	4612	Patients consulting for a suspicion of DHR	Children and adults ^a	26 (0.56%)	ST, DPT	MDH to drugs given simultaneously during the SCAR episode MDH was frequent in DRESS (18% of the positive DRESS cases) Congress communication	Antibiotics, NSAIDs, iRCM, corticosteroids, antiepileptics, analgesics
Mean age 55.1 years; range 16–78 years								
Gex-Collet <i>et al.</i> , 2005 [18]	Delayed-type DHR	7	Patients (adults) with proven of DHR	Adults ^b	7	ST, LTT	MDH cases are retrieved from a large database MDH to drugs given sequentially The authors propose 2 types of MDH: with simultaneous and sequential sensitization to drugs	Antibiotics, antiepileptics, hypnotics, antidepressants, local anesthetics, corticosteroids
Range 36–80 years								
Hari <i>et al.</i> , 2001 [17]	Delayed-type DHR	22	Patients (adults) consulting for a suspicion of DHR	Not specified ^a	2 (9%)	ST, LTT	The authors conclude that ST and LTT positivity in these 2 patients might prove true sensitisation to 2 different drugs taken during the same DHR	Antibiotics

Table 1 (Continued)

Author/year of publication	Clinical histories of tested patients	Number of tested patients	Studied population	Type of studied population	Patients with confirmed MDH [number (%)]	Drug allergy work-up	Comments	Drugs involved (from the most to the least prevalent ones)
Kanny <i>et al.</i> , 2005 [21]	Delayed-type DHR	12	Patients (adults) with proven DHR to iRCM	Adults ^a	6 (50%)	ST, LAT/LTT, immunohistology	1 patient with MDH to 3 different drug classes	(along with iRCM) Antibiotics, corticosteroids, antihistamine H1, antiparasitics
Mean age 57 years								
Range 19–83 years								
Studer <i>et al.</i> , 2012 [20 ^b]	Immediate and delayed-type DHR	1925	Patients (adults and children) consulting for a suspicion of DHR	Adults ^a	11 (0.6%)	ST, DPT	MDH cases are retrieved from a large database	Antibiotics, iRCM, proton pump inhibitors, anticoagulants, antivirals, antiepileptics, vasoconstrictors, corticosteroids, antihistamine H1, local anesthetics, antidopaminergic drug, vaccines
Mean age 62 years								
Range 28–79 years								
Sullivan <i>et al.</i> , 1989 [7]	Immediate-type DHR	437	Patients consulting for a suspicion of DHR to penicillins	Not specified ^a	4 (1%)	Not mentioned	This congress communication is considered to be the first report of documented MDH	Antibiotics

AGEP, acute generalised exanthematous pustulosis; DHR, drug hypersensitivity reaction; DPT, drug provocation test; DRESS, drug reaction with eosinophilia and systemic symptoms; iRCM, iodinated radiocontrast media; LAT, lymphocyte activation test; LTT, lymphocyte transformation test; MDH, multiple drug hypersensitivity syndrome; NA, not applicable; NSAIDs, nonsteroidal antiinflammatory drugs; SCAR, severe cutaneous adverse reaction; SD, standard deviation; SJS/TEN, Stevens Johnson syndrome/toxic epidermal necrolysis; ST, skin tests.

^athe studied population includes, but is not restricted to MDH patients.

^bthe studied population is restricted to MDH patients.

- (1) sensitization (as proven by either positive skin tests or LTT) is persistent and detectable for many years after the allergic reaction [18,19,22^{***}]. This is in agreement with other studies, showing the long-lasting persistence of T-cell memory versus IgE hypersensitivity [26]. In this respect, drugs taken at the same time as the initial DHR were able to elicit a new DHR (either less or just as severe), years after the initial reaction occurred;
- (2) proven sensitization to three different drug classes has been described;
- (3) antimicrobials or antiepileptics are often involved, but neosensitizations also involve drugs given as concomitant therapy. In order to study MDR, Barbaud *et al.* [22^{***}] tested all drugs introduced within 10 days prior to the onset of SCAR for AGEP, or within 2 months prior to onset for DRESS and SJS /TEN, as well as those introduced in the week following onset. Not surprisingly, proton-pump inhibitors or analgesic drugs were involved [19,22^{***}], as one would have expected in a syndrome which mimics an acute infection before full DRESS symptoms are displayed;
- (4) certain drugs given during DRESS management are well tolerated later on [19]. They may however be poor immunogens, not giving rise to reactive metabolites able to hapteneise proteins and activate specific T-cells.

CONCLUSION

The prevalence of MDH may be underestimated by the fact that not all suspected DHR are subject to, or can be proven following a full drug allergy work-up. This is due to both a lack of referral of patients with suspected DHR to specialised centres, as well as indications/contraindications and limitations of current allergy testing [22^{***},27].

However, practitioners should be aware of MDH and of the fact that for at least one subgroup of patients, circumstances of onset (such as a history of SCAR) seem to stand out quite clearly. In light of emerging knowledge regarding MDH, it seems highly recommended that the drugs prescribed for a patient with suspected SCAR, particularly DRESS, should be kept to a minimum. A thorough assessment of the drugs administered during a SCAR episode should be mandatory, in order to pinpoint those possibly involved in the DHR.

Moreover, bringing together the experience of the groups involved in the field of drug allergy should help to move forward the knowledge regarding this peculiar form of drug hypersensitivity.

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None.

Conflicts of interest

The authors declare no conflicts of interest for this work.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

■ of special interest

■ of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 452).

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