Original Article

Multiple Drug Hypersensitivity - proof of multiple drug hypersensitivity by patch and lymphocyte transformation tests

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Summary. *Background:* Multiple drug hypersensitivity (MDH) was first described in 1989 by Sullivan et al. as drug allergies to two or more chemically different drugs. So far, the diagnosis of MDH was associated almost exclusively with antibiotics and was defined based on history alone.
Aims of the study: The objective of this study was to prove MDH by two independent tests, namely patch (PT) and lymphocyte transformation (LTT) tests.
Methods: Here we present 7 patients matching the definition of a MDH which were documented by positive LTT as well as PT to different drugs.
Results: Three of the 7 patients developed sensitization to the different compounds during the same treatment period and had one longer-lasting allergic reaction. For another 4 patients sensitization to the different drugs occurred at distinct time points.
Conclusions: Our data support the concept of a MDH syndrome. The multiple sensitizations can be proven by skin and in vitro tests. We propose two subtypes of MDH: MDH, which develops against different drugs given *simultaneously*, and a second subtype, where the sensitizations develop *sequentially*. Antibiotics are often involved, but we also found sensitization to antiepileptics, hypnotics, antidepressants, local anesthetics, corticosteroids and other drug classes.

Key words: lymphocyte transformation test, multiple drug hypersensitivity, patch test, sequential sensitization, simultaneous sensitization to drugs.

Background

Multiple drug hypersensitivity (MDH) was first described in 1989 by Sullivan et al. [1] as drug allergies to two or more chemically different drugs which were mainly antibiotics. The clinical symptoms of the various drug allergies could differ (e.g. maculopapular exanthema to sulfonamide and anaphylaxis to a cephalosporin). So far MDH has rarely been described, it comprised almost exclusively allergies to antibiotics and was defined based on history alone or skin tests to penicillins.

Methods

Here we present 7 patients matching the definition of a MDH. They are documented by two independent tests, namely positive lymphocyte transformation test (LTT) [2] and patch tests to different drugs (Figure 1) [3]. The tests were performed at least six weeks after the patients had recovered from their allergic reactions, sometimes even many years after the first reaction. None of the patients included reacted to negative control substances like phosphate buffered saline (PBS) or vaseline. The drugs were used in concentrations which

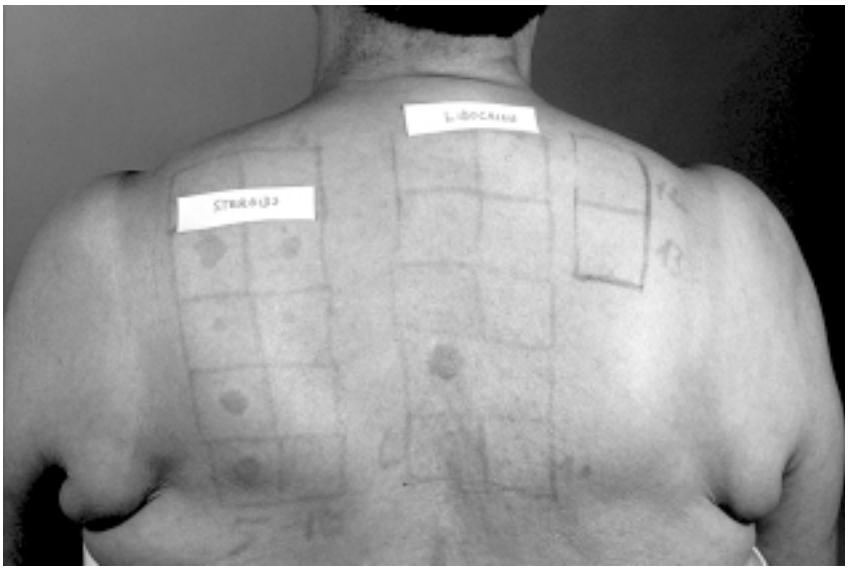

Figure 1. Positive patch test to lidocaine and corticosteroids (Amcinonid, Betamethason-17-valerat, budesonide, Clobetaso-17-propionat Hydrocortison-17-butyrat, Triamcinolonacetonid).

gave negative results in 20 control individuals [4]. Provocation tests were not made because of the risk of potential dangerous reactions.

Results

Three of the 7 patients developed sensitization to the different compounds (multi-therapy) at the same time and had one allergic reaction. For the remaining 4 patients the sensitizations to the different drugs occurred at distinct points in time, sometimes with a time interval of >10 years. Interestingly, skin or LTT was often positive even years after the allergic reaction, indicating that the sensitization was persistent and detectable for many years. In 5 of 7 cases aminopenicillins, namely amoxicillin (with or without clavulanic acid) were involved. Sensitization to sulfamethoxazol as well as to clarithromycin was found twice (patch test and/or LTT positive). Only once we found sensitizations (LTT and/or patch test positive) to metronidazol, ceftriaxon, triazolam, carbamazepine, phenytoin, fluvoxamine, lidocaine, budesonide, bismuthate and lansoprazole. The majority of patients with these positive tests had rather severe symptoms, namely bullous exanthemas, severe long-lasting and generalized maculopapular exanthema and drug-related eosinophilia with systemic symptoms (DRESS or severe drug hypersensitivity syndrome) (Table1). Normal controls did not react to the patch tests [4] and were also negative to these compounds in the LTT (1,10, 100 μg/ml).

Conclusions

Our data support the concept of a MDH syndrome. It can be proven by two independent tests, namely an in vivo test (skin patch test) and an in vitro test, the lymphocyte transformation test. These tests can persist for decades after the reaction (e.g. patient NN and FE, table 1). The second clinical manifestations may also occur after a long time interval.

We propose two subtypes of MDH: MDH, which develops against different drugs given *simultaneously*, and a second subtype, where the sensitizations develop *sequentially*, sometimes years apart. Antibiotics are often involved, but we also found sensitizations to antiepileptics, hypnotics, antidepressants, local anesthetics, corticosteroids and others. The culprit drugs are chemically unrelated and are metabolized through different pathways. Therefore there is no evidence of a possible cross-reactivity.

Patients with severe drug allergy symptoms may have a higher chance to develop a second drug allergy. In a former study done in our clinic 44 patients with a highly suggestive history of drug allergy and positive LTT had skin patch test and were well documented [5]. In this collective 4 patients showed sensitizations to more than one drug. So we estimate that up to 10% of patients with severe and well documented immune-mediated drug hypersensitivity have a tendency for this multiple drug hypersensitivity syndrome, which we interpret as a deficient ability to develop a tolerogenic immune response to xenobiotics [6]. A similar situation may prevail in patients who show contact dermatitis to different compounds like nickel, p-phenylendiamine etc. This implies that patients with a previous severe drug hypersensitivity may be at higher risk for another drug allergy and should be carefully supervised if they receive treatments with potentially sensitizing compounds like antiepileptics or certain antibiotics. Indeed, in a recent study of 12 patients with well documented delayed hypersensitivity to radio contrast media, six patients had had previous drug allergy [7].

Table 1. Clinical histories, incriminated compounds and positive test results (skin tests and LTT). SI: Stimulation index indicating the x-fold increase of the proliferation in cell cultures with drug compared to cultures without drug [2].

	Patients	Age	Clinic	Drug	Patch [48-72 hours] (concentrations in % in PBS)	LTT (SI)
simultaneous	B.M. (f)	80 y	bullous linear IgA-dermatosis	Metronidazol	pos. +++ (12,5)	5.5
				Clarithromycin	neg. (12,5)	3.2
				Paracetamol		1.9
				Furosemid	neg. (12,5)	2.6
				Mefenaminacid	neg. (12,5)	
				Lorazepam	neg. (12,5)	
				Ceftriaxon	pos. +++ (12,5)	21.7
	V.F. (m)	65y	maculo-papular dermatitis after Amoxicillin/ Clavulanic acid and Triazolam	Amoxi/Clav.Acid	pos. +++ (12,5)	
				Penicillin G		210
				Amoxicillin	pos. +++ (12,5)	18.8
				Clavulanic acid		11.7
				Ampicillin		44
				Triazolam	pos. +++ (12,5)	5.5
	S.F. (m)	43y	bullous exanthema after Amoxicillin/ Clavulanic acid and Trimryhoptin/ Sulfamethoxazol	Amoxi/clav. Acid	pos. +++ (12,5)	
				Penicillin G	pos. +++ (12)	13.1
				Amoxicillin	pos. +++ (12,5)	10.3
				Ampicillin		
				Paracetamol	neg. (12,5)	
				Lorazepam	neg. (12,5)	
				Trimeth./Sulfameth.	neg. (12,5)	
				Trimethoprim	neg. (12,5)	1.4
				Sulfamethoxazol	pos. +++ (12,5)	3.2
sequential	F.E. (f)	38y	gen. exanthema and fever	Penicillin G	pos. ++ (12)	24
				Ampicillin		2.6
		46y	maculo-papular dermatitis and dyspnea	Bismuthate	pos. +++ (12,5)	10.9
				Clarythormycin	neg. (12,5)	2.2
				Lansoprazole	pos. + (12,5)	9
				Trimethoprim	neg. (12,5)	1.7
				Sulfamethoxazol	neg. (12,5)	1.4
				Ranitidine	neg. (12,5)	1.9
	N.N. (f)	ca. 20y	exanthema	Penicillin G	neg. (12)	2.8
		40y	DRESS	Carbamazepine	pos. ++ (20)	28.5
				Oxacarbazepine	pos. + (12.5)	6
				Fluvoxamine	pos. + (12,5)	6.9
	O.F. (m)	36y	contact dermatitis	Lidocaine	pos. +++ (12,5)	56.7
				Cinchocaine	neg. (12.5)	0.8
				Bupivacaine	neg. (12.5)	
				Procaine	neg. (12,5)	
		46y	contact dermatitis	Budesonide	pos. +++ (0.1)	5.1
				Hydrocortisone	neg. (0.1)	0.6
	Z.W. (m)	60y	DRESS	Phenytoin	neg. (12,5)	72.5
		60y	DRESS	Sulfamethoxazol	neg. (5% in vas.)	24.6
				Trimethoprim	neg. (5% in vas.)	1.8

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