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Delayed corticosteroid hypersensitivity: a clinical management proposal

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Key words

Steroid allergy; delayed hypersensitivity; drug allergy; systemic contact dermatitis; allergic contact dermatitis.

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Summary

Background. *Different clinical pictures are related to corticosteroids (CS) non immediate hypersensitivity and the frequency of these reactions can be underestimated. The classification of CS in 3 groups and the identification of two patient's profiles has been proposed by Baeck to help clinicians in the management of these cases.* ***Methods.*** *Data of 14 patients with clinical history of delayed reactions to various CS and positive skin test and/or oral challenge are retrospectively analyzed.* ***Results.*** *Three different patterns of patients are identified evaluating history, clinical picture and tests results. The first one (6 pts, 43%) is characterized by cutaneous and/or mucosal reaction due to inhaled Budesonide and patch test positive only to topical molecules belonging to the group 1 of CS. The second pattern (4 pts) has clinical history of local and systemic skin reactions to the topic and parenteral administration of the same or other steroid drugs. Patients belonging to the third pattern (4 pts) have a history of systemic reactions to general administration of CS without previous contact reaction. Patterns 2 and 3 show a wide sensitization to molecules belonging to the 3 groups of CS. All the patients show patch test positive to Budesonide.* ***Conclusions.*** *Although the lack of standardization, the allergy workup proves useful to differentiate patients sensitized to one or few molecules from polysensitized and to identify the culprit drugs. Intradermal and challenge test are necessary to complete the diagnostic workup. The results suggest the possibility of a different management of patients. Patients of pattern one can be only patch tested with a limited series of CS belonging to the 3 groups. They don't need an extensive exclusion of steroids use. The pattern 2 and 3 must be submitted instead to a complete allergological individual evaluation to identify alternative tolerated drugs, because of the risk of systemic reactions. The Baeck's classification shows limited usefulness in these cases.*

Introduction

Although it seems a paradox, several cases of allergy to corticosteroids (CS) are described and both the IgE-mediated and the cellular type IV mechanisms are involved, causing immediate and delayed hypersensitivity reactions (1, 2) respectively. Steroids hypersensitivity is rare despite their wide use, in particular immediate reactions for which the prevalence is 0.1-0.3% (3); delayed reactions are more frequent with prevalence being 0.1-5% (4). However, the reactions could be under-diagnosed, since the clinical presentation can be sometimes confused with the disease requiring the steroid treatment. Delayed reactions can be due to topical application (allergic contact dermatitis, ACD) or can be the consequence of systemic administration of steroid to a patient previously sensitized. This is known as systemic contact dermatitis (SCD) and it can affect the 5% of cases with CS contact allergy (4).

Every CS molecule can cause sensitization and both topic and systemic administration can elicit symptoms. Three generations of steroids, in addition to cortisol (hydrocortisone) and cortisone (11-deidrocortisol) are available. The first classification (Coopman 1989) in 4 groups in function of their structure and contact-allergenic properties, has been modified by Baeck in 2011 into three groups (5) (**table I**). Steroids belonging to

group 1 are more prone to cause hypersensitivity due to the absence of C_{16}-methyl substitution and non-halogenation leading to an easier link to proteins and consequent aptenization. In the same study, Baeck identified two profile of patients: profile 1, patients who react to steroids from one group only, for whom the cross-reaction seems due to electrostatic fields and profile 2, patients who react to two or three groups because of the immunological recognition of the whole skeleton structure of steroid molecule (5). How this classification is useful in the clinical practice for predicting reactions is not clear. In fact, the cross-reactivity among steroids is important for delayed reactions, while less is known for immediate ones. Moreover, due to the lacking guidelines, the standardisation of diagnostic tests is still a problem.
The study retrospectively describes 14 cases of different delayed reactions, with the aim to better understand how to manage these patients in the clinical practice.
Secondary purpose is to compare the clinical pattern of these patients with the two patients profiles proposed by Baeck (5).

Materials and methods

Data of 14 patients with delayed steroid reactions confirmed by positive skin test and/or oral challenge were retrospectively collected. The mean age of the group was 60 years, nine were female. Written informed consent was obtained from each patient. Almost all patients (13 out of 14) had been patch tested with the CS molecules listed in **table II**, representative of the three groups of steroids according to the Baeck classification (5), with the addition of other drugs based on the individual clinical history. Standardized extracts for patch test were available only for a few molecules (Budesonide, Hydrocortisone 17 and 21, Desametasone), while for the others the commercial drugs were used according to the European guidelines criteria (6). The subsequent diagnostic process was personalized on the history and the clinical feature of each patient. Ten patients underwent to skin prick test (SPT), intradermal test (ID) with immediate and late reading (until 96 hours) and oral challenge (OC) for one or more drugs (7).

Table I *- Corticosteroid classification. Adapted from Baeck (5).*

Group 1	Group 2	Group 3
Budesonide	Triamcinolone	Alclometasone dipropionate
Cloprednol	Amcinonide	Beclomethasone dipropionate
Cortisone acetate	Desonide	Betamethasone
Dichlorisone acetate	Fluchloronide	Betamethasone 17-valerate
Difluprednate	Flumoxonide	Betamethasone dipropionate
Fludrocortisone acetate	Flunisolide	Betamethasone sodium phosphate
Fluorometholone	Fluocinolone	Clobetasol propionate
Fluprednisolone acetate	Fluocinonide	Clobetasone butyrate
Hydrocortisone	Halcinonide	Desoximetasone
Hydrocortisone aceponate	Triamcinolone acetonide	Dexamethasone
Hydrocortisone acetate	Triamcinolone benetonide	Dexamethasone acetate
Hydrocortisone 17-butyrate	Triamcinolone diacetate	Dexamethasone sodium phosphate
Hydrocortisone 21-butyrate	Triamcinolone hexacetonide	Diflucortolone valerate
Hydrocortisone hemisuccinate		Diflorasone diacetate
Isofluprednone acetate		Flumethasone pivalate
Mazipredone		Fluocortin butyl
Medrysone		Fluocortolone
Methylprednisolone acetate		Fluocortolone capraylate
Methylprednisolone aceponate		Fluocortolone pivalate
Methylprednisolone hemisuccinate		Fluocortolone acetate
Prednicarbate		Halometasone
Prednisolone		Meprednisone
Prednisolone caproate		Fluticasone propionate
Prednisolone pivalate		Mometasone furoate
Prednisolone sodium metasulfobenzoate		
Prednisolone succinate		
Prednisone		
Tixocortol pivalate		

Table II *- Panel of steroids used for patch test.*

Group 1	Group 2	Group 3
Budesonide	Triamcinolone acetonide	Betamethasone dipropionate
Hydrocortisone	Flunisolide	Betamethasone sodium-phosphate
Hydrocortisone 17 butyrate		Desoxymethasone
Hydrocortisone 21 butyrate		
Methylprednisolone acetate		
Methylprednisolone hemisuccinate		
Prednisolone		

Table III *- Characteristics of patients belonging to the Pattern 1.*

N°	Age	Sex	Culprit drug	Clinical presentation	Positive patch test	Intradermal test	Oral challenge
1	55	F	Budesonide aerosol	Face and neck erithema and oedema	**Budesonide Hydrocortisone-21-acetate**	Hydrocortisone succinate negative	Prednisone negative
2	36	F	Budesonide aerosol	Face and neck erithema Lips oedema	**Budesonide**	Betamethasone phosphate negative	Deflazacort negative
3	23	F	Budesonide aerosol	Oral and face oedema	**Budesonide Hydrocortisone- 17 butyrate**	N. D.	N. D.
4	42	F	Budesonide aerosol	Lips oedema Stomatitis	**Budesonide Hydrocortisone- 17 butyrate**	N. D.	N. D.
5	49	M	Nasal Budesonide	Face oedema and mucosal oedema	**Budesonide**	Betamethasone phosphate negative	Betamethasone phosphate negative
6	58	F	Budesonide aerosol	Lips oedema	**Budesonide**	N. D.	N. D.

The culprit drug is underline when positive; N.D.: not done.

Results

According to clinical history, culprit drugs and test results, the patients were divided into three patterns.

Pattern 1 (see table III)

Six patients with local reaction of various degree of severity appeared after Budesonide bronchial inhalation (5 cases) or nasal spray (1 case).
Patch test confirmed the causal relationship with Budesonide. The cross-reactivity was limited to a few molecules belonging to the same group of CS such as Hydrocortisone 17-butyrate and Hydrocortisone 21-acetate, both used locally. Prick test, ID and oral challenge test performed with a set of different molecules resulted negative for three patients.

Pattern 2 (see table IV)

Four patients with a history of ACD due to steroids other than Budesonide, for topic skin use. Two of them presented systemic skin reactions after parenteral administration of other steroids. Patch test showed a wide polisensitization in three patients. Patient number 7 underwent intradermal test only (negative for the culprit but positive for a not suspected molecule) while oral challenge protracted for two days was necessary to confirm the history of systemic dermatitis elicited by oral desamethasone.

Pattern 3 (see table V)

Four patients with systemic delayed urticaria or exanthema after administration of different systemic drugs, without any previous local reaction to topical products.

Table IV *- Characteristics of patients belonging to the pattern 2.*

N°	Age	Sex	Culprit drug and administration route	Clinical presentation	Positive patch test	Intradermal test	Oral challenge
7	77	M	**Topical** not known **Desamethasone** oral	Allergic Contact dermatitis Systemic dermatitis	N. D.	**M- prednisolone positive** Desamethasone negative	**Desamethasone positive**
8	75	F	**Betamethasone valerate** topical **Betamethasone Na- phosphate** parenteral	Allergic Contact dermatitis Diffuse Erithema	**Budesonide** **Beclomethasone** **Fluocinolone a.** **Flunisolide** **Triamcinolone a.**	**Betamethasone phosphate positive** Prednisone negative M- prednisolone negative	Prednisone negative
9	62	F	**Topical** drugs not known	Allergic contact dermatitis	**Budesonide** **Betamethasone valerate** **Betamethasone dipropionate** **Deflazacort** **Desamethasone** **Diflucortone** **Hydrocortisone** **M-prednisolone** **Triamcinolone**	N. E.	N. E.
10	62	F	**Betamethasone valerate** topical	Allergic contact dermatitis	**Betamethasone valerate dipropionate** **Na phosphate** **Beclomethasone** **Budesonide** **Desamethasone** **Diflucortolone** **Hydrocortisone 17 butyrate** **Prednisolone** **Triamcinolone**	Betamethasone Na Phosphate negative M- prednisolone negative	Prednisone negative

The culprit drug is underline when positive; N.D.: not done.

They showed wide sensitization to the patch test panel, comprehensive of the suspected drug, while intradermal test was negative to the culprit drug in three cases and challenge test gave doubtful results.

Discussion

Drug allergy reactions to steroids are not so rare, mainly the delayed ones. Allergic contact dermatitis is the most frequent clinical picture: it has to be considered in patients using cutaneous topical steroids with worsening of dermatitis and also in patients using inhaled steroid and developing mucositis, cutaneous eczema or angioedema involving nasal or oral mucosa, lips, face and neck. Moreover, a systemic cutaneous reaction can be caused by systemic administration, even after a single dose of steroid drug, used for example for intra-articular injection (1, 2, 4, 8).

The cases analyzed in this study confirm that delayed hypersensitivity to CS can be caused by different patterns of sensitization and can occur with different clinical picture. One of the most frequent (pattern 1: 43%) is the muco-cutaneous reaction to inhaled products, with Budesonide resulting the sensitizer molecule and a cross-reactivity limited to a few similar topical steroids, belonging to the same group. The clinical consequence is that these patients don't seem to be prone to develop systemic reactions and usually they should not limit the use of steroids. In the second group of patients a previous local reaction to a cutaneous product can lead

Table V *- Characteristics of patients of pattern 3.*

N°	Age	Sex	Culprit drug and administration route	Clinical presentation	Positive patch test	Intradermal test	Oral challenge
11	68	M	**Triamcinolone intraarticular**	Delayed urticaria	**Triamcinolone** **Desamethasone** **Diflucortolone** **Betamethasone Na phosphate** **Betamethasone valerate** **Betamethasone dipropionate** **Budesonide** **Hydrocortisone 17 butyrate** **M-prednisolone a** **M- prednisolone s.**	**M- prednisolone positive** Prednisone negative Triamcinolone negative Betametasone Na phosphate negative	**Prednisone negative**
12	81	M	**Betamethasone Na phosphate** intraarticular	Delayed urticaria	**Betamethasone** **Budesonide** **Beclomethasone** **Desamethasone** **Diflucortone** **Fluocinolone** **Flunisolide** **Hydrocortisone** **Methylprednisone** **Triamcinolone**	**Betametasone Na phosphate positive** M- prednisolone hemisucinate negative	Deflazacort doubtful
13	71	F	**M-prednisolone** parenteral **Deflazacort** oral	Diffuse exanthema	**Budesonide** **Hydrocortisone 17 butyrate** **Deflazacort**	M- prednisolone negative Betametasone Na phosphate negative	Betametasone Na phosphate negative
14	76	M	**Betamethasone Na-Ph** parenteral **Desamethasone** oral **Beclomethasone** rectal	Urticaria Immediate rash Urticaria	**Budesonide** **Beclomethasone** **M- prednisolone**	M- prednisolone negative Betametasone Na phosphate negative	Prednisone doubtful

The culprit drug is underline when positive; N.D.: not done.

to systemic symptoms when the drug is administered by systemic route; this could be triggered even by drugs different from the sensitizer. These patients show sensitization to a wide range of molecules belonging to different chemical groups of CS.

The third pattern is characterized by a history of delayed urticaria or exanthema after systemic administration of various steroid drugs by different route (oral, intra-articular, intramuscular, rectal). No previous topical reactions are reported and patients show sensitization to many molecules over the culprit. All the patients are sensitized to Budesonide even in the absence of previous contact.

Similarly to other studies (9), this report confirms the validity of the Baek's hypothesis: some patients seem to recognize only the lateral chain of the steroid molecule with limited cross-reactivity, while others seem to recognize the skeletal structure of the molecule, with wide cross-reactivity. Some further differences among these patients can be identified in the clinical history, in the way of sensitization and in test results.

This may suggest different management of patients: pattern 1 may have a few limitations related on the use of topical molecules only. For the two other patterns, due to the broad sensitization spectrum, it's necessary to find one or more alternative molecules to avoid the risk of systemic reactions.

As usual in drug allergy, the diagnostic workup depends on the way of administration of the drugs and the timing of onset of symptoms. The choice of the drugs to be tested depends on the clinical history and on the need of individual patient. Unfortunately, the diagnostic workup is not standardized yet. Moreover, the anti-inflammatory activity of CS can reduce the sensitivity, requiring different kinds of test (patch, intradermal and challenge test) to confirm the role of the drug as cause of reaction.

Conclusions

The results of this study show that in the clinical practice it's important to set up a workup tailored to the pattern of patients, evaluating multiple molecules for the assessment of the individual sensitization/tolerance profile. The classification of steroids in chemical groups appears to be of limited usefulness, due to the great variability of reactivity and sensitization of the patients. Moreover, it's not applicable to systemic corticosteroids and does not seem to be useful to predict SCD (10, 11).
The study has some limitations, mainly as a consequence of its retrospective design and the limited number of patients.
Nevertheless, studies like this could increase awareness of steroids hypersensitivity reactions and help clinicians on the management (11).

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Conflict of interests

The authors declare that they have no conflict of interests.

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