METABOLIC, INFLAMMATORY AND OTHER UNRAVELED MARKERS IN DRUG ALLERGY

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Porto, 2021

Tese de Candidatura ao grau de Doutor em
Farmacologia e Toxicologia Experimentais e Clínicas
apresentada à Faculdade de Medicina da Universidade do Porto

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Ao abrigo do Artigo 8° do Decreto-Lei n°388/70, fazem parte desta dissertação as seguintes publicações:

- Dias de Castro E, Carolino F, Ribeiro L, Cernadas JR. Overview of Drug Allergy: From Immunogenetics to Practice. *Acta Med Por* 2018 Oct; 31(10):581-588.

- Dias de Castro E, Carolino F, Carneiro-Leão L, Barbosa J, Ribeiro L, Cernadas JR. Allergy to beta-lactam antibiotics in children: Risk factors for a positive diagnostic work-up. *Allergol Immunopathol (Madr)*. 2020; 48(5):417-423.

- Dias de Castro E, Leblanc A, Barbosa J, Ribeiro L, Cernadas JR. Psychological profiles of patients with suspected drug allergy. *Asia Pac Allergy.* 2020 Oct;10(4):e39.

- Dias de Castro E, Barbosa J, Mesquita AM, Caires A, Ribeiro L, Cernadas JR, Baiardini I. Hypersensitivity Quality of Life Questionnaire: Validation procedures and first results of the Portuguese version. *Health Qual Life Outcomes* 2021 May 10; 19 (1): 143.

- Dias de Castro E, Pinhão S, Paredes S, Cernadas JR, Ribeiro L. Obesity markers in patients with drug allergy and body fat as a predictor. *Ann Allergy Asthma Immunol* 2021 Jul; 127 (1):100-108.

- Dias de Castro E, Pinhão S, Paredes S. Cernadas JR, Ribeiro L. Dietary parameters in patients with drug allergy: assessing dietary inflammatory index (submitted).

“Science is not only a discipline of reason,

but also one of romance and passion”.

Stephen Hawking

À minha família

Agradecimentos

À minha orientadora e amiga Professora Laura Ribeiro, pelo desafio que me lançou a candidatar-me a este Programa Doutoral. Também pelo apoio incondicional, pela orientação entusiasta, atenta e inteligente, durante todo este percurso. A amizade começou antes mesmo dos tempos da Faculdade e sai reforçada, no final desta aventura.

Ao Professor Daniel Moura por ter liderado a criação deste Programa Doutoral e por me ter incentivado a integrar o primeiro curso. Agradeço, também, por nos ter acompanhado com dedicação, carinho e entusiasmo, durante cada minuto do ano letivo deste Programa.

Ao Professor Patrício Soares da Silva, coordenador do Programa Doutoral, pela supervisão atenta e pelo incentivo durante todo este percurso, em particular nos momentos decisivos.

Ao Serviço de Imunoalergologia, sem o qual não poderia realizar este trabalho. A todos os colegas, em particular à Dra. Josefina Cernadas, minha coorientadora e responsável da Área Específica de Alergia a Fármacos, pela orientação, partilha de experiência e conhecimento nesta área tão desafiadora da especialidade. Ao Diretor de Serviço, Dr. José Luís Plácido, pelo apoio constante, logo desde a decisão da candidatura. Agradeço ainda, especialmente, à Dra. Alice Coimbra pelo apoio, pela amizade, pela alegria contagiante e pela revisão final do inglês deste trabalho.

A todos os doentes que colaboraram neste trabalho e foram elementos imprescindíveis para a sua realização.

À equipa de enfermagem do Hospital de dia e à Dra. Alice Cortez, pela colaboração, pela inteira disponibilidade e carinho.

À Professora Sílvia Pinhão, à Professora Joselina Barbosa e à Dra. Sílvia Paredes por terem colaborado de forma entusiasta, com empenho e disponibilidade neste desafio.

Às minhas amigas de sempre, Cristina, Carla, Hélia e Isabel, por me apoiarem sempre e incondicionalmente, nos diversos desafios que a vida me foi trazendo, por me desejarem sempre o melhor. À Carla, pelo apoio e pelas palavras de incentivo, nos momentos mais difíceis e que muito me ajudaram a não desistir deste desafio, em particular.

Ao Andrés, por me apoiar ao longo deste percurso, por me incentivar a manter sempre a curiosidade, o gosto pelo conhecimento, a persistência e a resiliência.

Aos meus sobrinhos Filipa, Guilherme e Miguel, pelo amor, pela ternura e pela alegria.

À minha família, em particular aos meus pais e aos meus irmãos, pelo incentivo constante e por acreditarem sempre em mim. Por valorizarem o amor, a amizade, a verdade e a empatia. Ainda aos meus pais, por me terem dado as ferramentas para encarar os diversos desafios da vida e me transmitirem que o trabalho e dedicação trazem sempre resultados.

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Abstract

Drug therapy is often a balance between the beneficial and harmful effects of drugs demanding a risk-benefit assessment. Drug allergic reactions are adverse drug reactions mediated by immunological mechanisms. Given the heterogeneity, unpredictability and the potential severity of drug allergy, the management of these type of reactions is particularly challenging. Nonetheless, exposure to a particular drug induces immune reactions in only a minority of individuals. The identification of subjects at high risk is crucial. It might prevent reactions to occur, allowing to adjust the drug allergy diagnostic protocols according to the patient´s risk. It is also important to comprehend the impact that drug allergy may have on the patient's quality of life.

Furthermore, the incidence of drug allergy is consistently increasing in line with an overall increasing incidence of allergic diseases. This is especially reported in developed countries and some factors of a westernized lifestyle have emerged as potential contributors.

The overall aim of this thesis was to investigate whether individual factors such as demographic, psychological characteristics, metabolic and/or inflammatory factors are associated with a higher susceptibility to drug allergy.

Obesity and dietary parameters in patients with drug allergy were assessed for the first time. Patients with drug allergy revealed significantly higher parameters associated with both global and central obesity, measured by anthropometry and bioimpedance, than controls. They also presented higher levels of systemic inflammatory markers such as serum leptin and leptin-adiponectin ratio. Those with immediate reactions to drugs also revealed significantly higher obesity traits. Moreover, the logistic regression analysis revealed body fat percentage as a predictor of drug allergy and immediate reactions to drugs. Although patients with drug allergy revealed higher obesity and inflammatory parameters, the dietary inflammatory index (DII) applied did not allow to distinguish between patients with drug allergy and controls, since both groups revealed an anti-inflammatory diet profile. The DII scores correlated with triglycerides levels in the drug allergic patients and inversely with adiponectin levels in the control group. New potential markers in drug allergy that can be modifiable through lifestyle interventions were unraveled. Improving obesity and inflammatory parameters might modify drug allergy outcomes along with global benefits in patient health.

In this investigation, the psychological characteristics of patients with drug allergy were assessed, based on validated questionnaires. These patients revealed more psychological disturbances, namely higher anxiety, higher neuroticism and lower extraversion, than healthy-

controls. Performing this assessment in clinical practice could help to identify patients that would benefit from psychological intervention.

The risk-factors for beta-lactam allergy in children were also investigated, since this is the main cause of drug allergy in this age group. We found, for the first time, that the likelihood of beta-lactam allergy was significantly higher in children family history of drug allergy. Genetic tests are needed to clarify this finding.

The translation and cross-cultural adaptation of the Drug Hypersensitivity Questionnaire to Portuguese and the evaluation of its psychometric properties were performed according to current guidelines, filling a gap in the assessment of Portuguese patients with drug allergy. It revealed adequate validity and reliability, and could discriminate patients according to clinical aspects. More severe reactions and a greater number of suspected drugs were predictors of worse quality of life.

Finally, throughout this research, clinical aspects of drug allergic reactions associated with a positive diagnostic work-up were investigated. Overall, we found that severe reactions, immediate reactions, higher number of reactions and a shorter elapsed time between reaction and study were associated with a higher likelihood of drug allergy.

Resumo

A terapêutica farmacológica consiste, frequentemente, num equilíbrio entre os efeitos benéficos e adversos dos fármacos. As reações alérgicas a fármacos são reações adversas imunologicamente mediadas. Dada a sua heterogeneidade, imprevisibilidade e potencial gravidade, a abordagem deste tipo de reações é particularmente desafiadora. Contudo, a exposição a um determinado fármaco induz reações imunológicas apenas numa minoria de indivíduos. A identificação dos indivíduos com elevado risco é crucial. Poderá prevenir as reações de ocorrerem, permitindo ainda ajustar os protocolos de diagnóstico de alergia a fármacos, de acordo com o risco individual do doente. É ainda importante compreender o impacto que a alergia a fármacos pode ter na qualidade de vida do doente.

Além disso, a incidência da alergia a fármacos tem vindo a aumentar consistentemente com o aumento global da incidência das doenças alérgicas. Este aumento tem-se verificado essencialmente nos países desenvolvidos e alguns fatores associados a um estilo de vida mais ocidental têm emergido como potencialmente implicados.

O objetivo global desta tese foi o de investigar se fatores individuais como fatores demográficos, características psicológicos, fatores inflamatórios e/ou metabólicos estão associados a uma maior suscetibilidade de alergia a fármacos.

Avaliamos, pela primeira vez, parâmetros de obesidade e da dieta nos doentes com alergia a fármacos. Os doentes com alergia a fármacos revelaram parâmetros significativamente mais elevados de obesidade global e central, determinados por antropometria e bioimpedância, comparativamente com os controlos. Também apresentaram marcadores de inflamação sistémica significativamente mais elevados, como níveis de leptina sérica e rácio de leptina-adiponectina. Da mesma forma, os doentes com reações imediatas revelaram maiores traços de obesidade. Acresce que a percentagem de massa gorda se revelou como um preditor de alergia a fármacos, particularmente de reações imediatas, na análise de regressão logística realizada.

Embora os doentes com alergia a fármacos apresentassem maiores parâmetros de obesidade e inflamação, o índice inflamatório da dieta (IID) aplicado não permitiu distinguir entre doentes com alergia a fármacos e controlos, tendo os 2 grupos revelado um padrão anti-inflamatório.

O IID correlacionou-se com os níveis de triglicerídeos, no grupo de doentes com alergia a fármacos e inversamente com os níveis de adiponectina, no grupo controlo.

Neste trabalho, foram desvendados novos potenciais marcadores na alergia a fármacos e que podem ser modificáveis através de intervenções no estilo de vida. Uma melhoria nos parâmetros de obesidade e inflamação poderão ter impacto na alergia a fármacos, para além dos benefícios globais na saúde do doente.

As características psicológicas dos doentes com alergia a fármacos foram avaliadas, através de questionários validados. Estes doentes apresentaram mais distúrbios psicológicos que os controlos saudáveis, designadamente maior ansiedade, maior neuroticismo e menor extroversão. Na prática clínica, este tipo de avaliação poderá ajudar a identificar os doentes que poderão beneficiar de intervenção psicológica.

Também investigamos fatores de risco associados a alergia a antibióticos beta-lactâmicos em idades pediátricas, uma vez que estes são a principal causa de alergia a fármacos nestes grupos etários. Reportamos, pela primeira vez, que a probabilidade de alergia a beta-lactâmicos foi significativamente maior nas crianças com história familiar de alergia a fármacos. Será importante realizar estudo genético para clarificar este resultado.

Realizamos ainda a tradução e adaptação transcultural do Questionário de Hipersensibilidade a Fármacos para a população portuguesa, bem como a respetiva avaliação das suas propriedades psicométricas, de acordo com as recomendações atuais. A versão portuguesa do questionário demonstrou validade e consistência adequadas, permitindo discriminar os doentes de acordo com aspetos clínicos e colmatando uma necessidade na avaliação dos doentes portugueses com alergia a fármacos. Neste estudo, as reações mais graves e um maior numero de fármacos suspeitos foram preditores de pior qualidade de vida.

Finalmente, ao longo deste trabalho, investigamos aspetos clínicos das reações alérgicas a fármacos potencialmente associados a um protocolo de diagnóstico positivo. Globalmente, as reações graves, as reações imediatas, um número maior de reações e um menor intervalo de tempo decorrido entre a reação e o estudo diagnóstico, associaram-se a uma maior probabilidade de confirmação de alergia a fármacos.

List of Abbreviations

ADR- Adverse drug reaction

DAR- Drug allergic reaction

ßL- Beta-lactam

IR- Immediate reaction

NIR- Non-immediate reaction

IgE- Immunoglobulin E

IgM- Immunoglobulin M

IgG- Immunoglobulin G

IC- Immune complexes

MPE- Maculopapular exanthema

SCAR- Severe adverse cutaneous reaction

SJS- Stevens-Johnson syndrome

TEN- Toxic epidermal necrolysis

DRESS- Drug reaction with eosinophilia and systemic symptoms

AGEP-Acute generalized exanthematous pustulosis

FDE- Fixed drug eruption

PEF- Peak expiratory flow

BP-Blood pressure

GBFDE- Generalized bullous fixed drug eruption

SDRIFE- Symmetrical drug-related intertriginous and flexural exanthema

Th- T helper

IFN-γ- Interferon gamma

IL- Interleukin

CXCL- Chemokine motif ligand

PRACTALL- Practical Allergy Report

EAACI- European Academy of Allergy and Clinical Immunology

AAAAI- American Academy of Asthma, Allergy and Immunology

THIQ - Tetrahydroisoquinoline

MRGPRX2- Mas-related G protein-coupled receptor-X2

HLA- Human leukocyte antigens

TCR- T-cell receptor

p-i- Pharmacological interaction

ENDA- European Network of Drug Allergy

SPT- Skin prick tests

IDT- Intradermal tests

DPT- Drug provocation test

BAT- Basophil activation test

LTT- Lymphocyte transformation test

HIV- Human Immunodeficiency virus

EBV- Epstein-Barr virus

CYP- Cytochrome P450

FceR1b -High affinity IgE receptor b chain

NAT2- N- acetyltransferase2,

GST- Glutathione- S-transferase.

PROs- Patient-reported outcomes

BFP- Body fat percentage

DII- Dietary inflammatory index

MUFAs- Mono-unsaturated fatty-acids

DrHy-Q - Drug Hypersensitivity Questionnaire

HRQoL- Health-related quality of life

CPARA- Portuguese Catalogue of Allergies and other adverse reactions

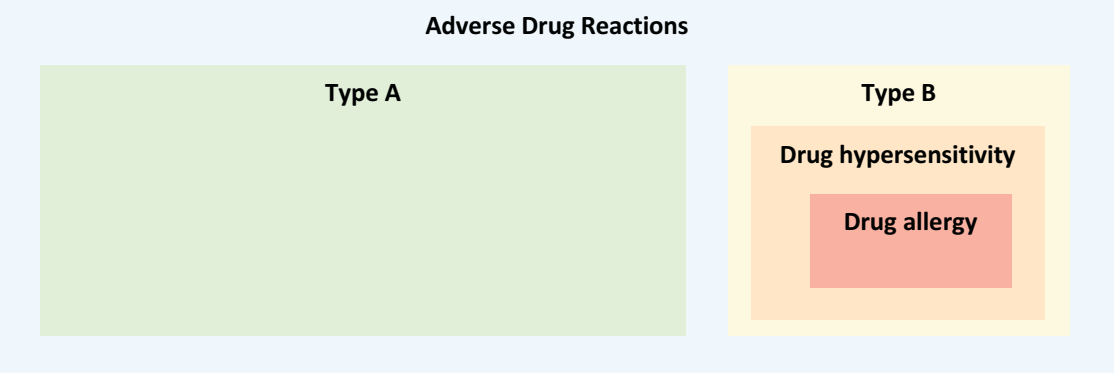
I. INTRODUCTION

1. DRUG ALLERGY

An adverse drug reaction (ADR) has been defined by the World Health Organization as any noxious, unintended and undesired effect of a drug occurring at doses normally used for prevention, diagnosis or treatment [1]. ADRs are categorized clinically as type A (predictable, common, related to the pharmacological properties of the drug) or type B (usually unpredictable and unrelated to the pharmacological actions of the drug). The first type includes side effects, drug-induced toxicity and drug interactions. The type B reactions represent 20% or less of ADRs and include drug allergic reactions (DARs), that are ADRs mediated by immunological mechanisms [2,3]. In practice, when it is not possible to demonstrate an immunological mechanism, the term drug hypersensitivity is used for drug reactions that clinically appear to be allergic.

DARs can be very complex and potentially severe, even life-threatening. The study of these reactions is challenging as these reactions have a great heterogeneity of clinical presentation, supported by different mechanisms [2]. It is constantly updated as new drugs are developed, new indications are established and drug consumption patterns are changed [4].

Figure 1- Adverse drug reactions



1.1. Epidemiology

There are no systematic epidemiologic studies of drug allergy. ICD-9 and ICD-10 codes are neither specific nor sensitive for identifying patients with the specificities of drug allergy [3]. A lack of knowledge on drug allergy epidemiology persists, particularly in children [5].

ADRs are estimated to account for 3% to 6% of all hospital admissions and to occur in 10% to 15% of hospitalized patients, contributing to significant morbidity, mortality and socio-economical costs [6,7]. The rates in paediatrics were found to be lower with 2% of children hospitalized for ADRs, and 9.5% experiencing ADRs during hospitalization [8].

Drug allergy is relatively less common accounting for approximately 6% to 10% of all ADRs [9,10], but its incidence is consistently increasing with an overall increasing incidence of allergic diseases [10]. From 2001 to 2012, the estimated incidence for emergency department visits for DARs rose from 0.49% to 0.94% [11]. Drug allergy occurs in approximately 1% to 2% of all hospital admissions and in 3% to 5% of hospitalized patients [10].

In a recent review from Brazil, 40% to 60% of all anaphylactic reactions treated in the emergency room were due to drug allergy [12].

Some studies indicate that among ADRs, drug allergy may be more common in children than in adults: more than 50% of all ADRs in paediatric inpatients and about 35% of ADRs in paediatric emergency care are thought to be allergic. Most drug reactions in children are still attributed to beta-lactam antibiotics (ßL antibiotics) [5]. In a Spanish study, 81% of the referred cases for suspected drug allergy in children where related to ßL antibiotics [13].

However, the true incidence of drug allergy in the community, both in children and adults remains unknown [9].

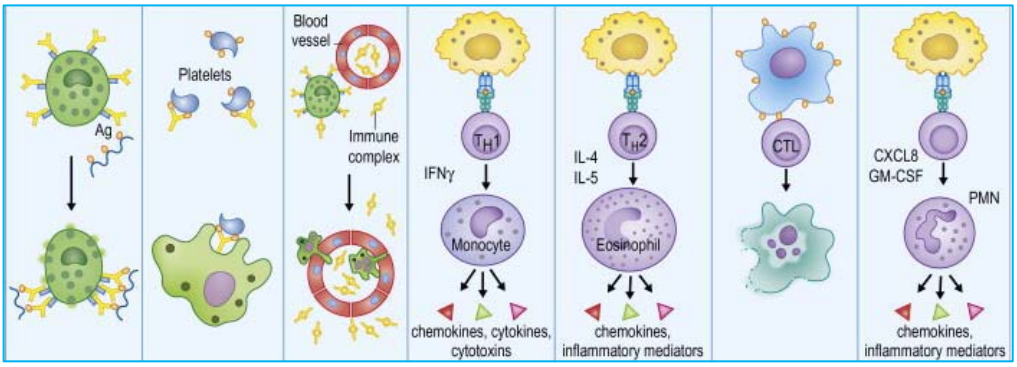
1.2. Classification

DARs are usually classified according to the clinical presentation or the underlying immunological mechanism [2,10]. Although, no single classification scheme allows the categorization of all DARs [10].

1.2.1. Immunological mechanisms

DARs are still classified based on the four immunological mechanisms proposed by Gell and Coombs. **Type I** involves immediate reactions mediated by IgE antibodies [2,10]. **Type II** are cytotoxic IgM- or IgG-mediated reactions against a cell surface antigen. **Type III** consists in immune complex (IC) deposition reactions involving complement activation. **Type IV** are mediated primarily by T cells [2,10] and have been recently classified in 4 subtypes, according to cytokine patterns and the preferential activation of different immunocytes [14] (Table 1). Some DARs cannot be classified according to the underlying mechanism, either due to lack of information or they do not fit into the present classification [10].

Figure 2- **Drug Allergy-Type of immune response** (adapted from 15)



Type I **Type II** **Type III** **Type IV a)** **Type IV b)** **Type IV c)** **Type IV d)**

1.2.2. Clinical Presentation

Clinically, DARs are classified depending on the time of the onset, as immediate or non-immediate.

Immediate reactions (IRs) occur within minutes up to one to 6 hours after drug administration, as a set of symptoms ranging from urticaria and angioedema to anaphylaxis (Box 1) [2,10].

Non-immediate reactions (NIRs) manifest after 6 hours, usually days or weeks after drug exposure, as isolated single-organ involvement or systemic multiorgan involvement [2,10]. The skin is the most frequently involved organ with a wide range of clinical presentations, from the most common and mild maculopapular exanthema (MPE) to the severe adverse cutaneous reactions (SCARs) such as Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug rash with eosinophilia and systemic symptoms (DRESS) and acute generalized exanthematous pustulosis (AGEP) [2,10,17].

Besides chronology, morphology and distribution of the skin lesions are also key points for the diagnosis. Associated symptoms and signs are also relevant [17].

Box 1: Definition and Clinical criteria for diagnosing anaphylaxis [16].

DEFINITION: Severe, potentially life-threatening systemic hypersensitivity reaction. It is characterized by rapid onset with life-threatening airway, breathing, or circulatory problems; usually, but not always, associated with skin and mucosal changes.

Anaphylaxis is highly likely when **any one of the following three criteria** is fulfilled:

1. Acute onset of an illness (minutes to several hours) with **involvement of the skin, mucosal tissue, or both** (e.g., generalized hives, pruritus or flushing, swollen lips–tongue–uvula)

AND AT LEAST ONE OF THE FOLLOWING

a. Respiratory compromise (e.g., dyspnea, wheeze–bronchospasm, stridor, reduced PEF, hypoxemia)

b. Reduced BP or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence)

2. Two or more of the following that occur rapidly after exposure to a **likely allergen for that patient** (minutes to several hours):

a. Involvement of the skin–mucosal tissue (e.g., generalized hives, itch-flush, swollen lips–tongue–uvula

b. Respiratory compromise (e.g., dyspnea, wheeze–bronchospasm, stridor, reduced PEF, hypoxemia)

c. Reduced BP or associated symptoms (e.g., hypotonia [collapse], syncope, incontinence)

d. Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)

3. Reduced BP after exposure to known allergen for that patient (minutes to several hours):

a. Infants and children: low systolic BP (age specific) or >30% decrease in systolic BP*

b. Adults: systolic BP of <90 mmHg or >30% decrease from that person's baseline

Notes:

*Low systolic blood pressure for children is defined as <70 mmHg from 1 month to 1 year, less than (70 mmHg + [2 9 age]) from 1 to 10 years and <90 mmHg from 11 to 17 years.

Legend: PEF- peak expiratory flow; BP- blood pressure.

In table 1 the classification of DARs is summarized and in table 2 the typical cutaneous manifestations are described.

Table 1- Classification of drug allergic reactions (adapted from 2).

Type	Type of immune Response	Pathophysiology	Time of reaction	Clinical symptoms	Typical chronology of the reaction
I	IgE	Mast cell and basophil degranulation	Immediate	**Anaphylaxis** **Urticaria/Angioedema** **Bronchospasm** **Rhinitis**	Between 1 to 6 h after the last drug intake

II	IgG and complement	IgG and complement-dependent cytotoxicity	Non-immediate	**Cytopenia**	5–15 days after the start of the eliciting drug
III	IgM or IgG and complement or FcR	Deposition of immune complexes		**Serum sickness** **Urticaria** **Vasculitis**	7–8 days after the start of the eliciting drug for serum sickness/urticaria; 7–21 days for vasculitis
IV a	Th1 (IFN—γ)	Monocytic inflammation		**Eczema**	1–21 days after the start of the eliciting drug
IV b	Th2 (IL-4 and IL-5)	Eosinophilic inflammation		**MPE** **DRESS**	1 to several days after the start of the eliciting drug for MPE; 2–6 weeks for DRESS
IV c	Cytotoxic T cells (perforin, granzyme B, FasL, granulysin)	Keratinocytic death mediated by CD4 or CD8		**MPE** **FDE** **SJS/TEN**	1–2 days after the start of the eliciting drug for FDE; 4–28 days for SJS/TEN
IV d	T cells (IL-8/CXCL8)	Neutrophilic Inflammation		**AGEP**	1–2 days after the start of the eliciting drug, but can be longer

Legend: **IgE**: Immunoglobulin E; **IgM**- Immunoglobulin M; **IgG**- Immunoglobulin G; **Th1**- T helper1; **Th2**-T helper 2; **IFN -γ**: Interferon gamma; **IL4-** Interleukin 4; **IL5**- Interleukin 5; **IL8**- Interleukin 8; **CXCL8**- Chemokine motif ligand 8

Table 2- Typical clinical manifestations of cutaneous drug allergic reactions (adapted from 17).

	Primary lesion and typical feature	Distribution	Important characteristics and other relevant symptoms, signs or complications
Urticaria	Wheals	Single or widespread	Eventually associated with angioedema; beware of anaphylaxis
Angioedema	Deep swelling	Usually face, less often extremities and genitals; usually asymmetric	Eventually associated with urticaria; beware of anaphylaxis
Vasculitis	Purpuric papules	Lower extremities primarily	Systemic organ involvement may occur; haemorrhagic and/or necrotic lesions; Histology: leucocytoclasia
MPE	Macules, papules	Trunk >extremities	Pruritus, low-grade- fever and eosinophilia may be present
DRESS	Variable: macules, papules, small superficial pustules, or vesicles, eczema-like, target-lesions, purpura	Face, upper trunk, extremities, widespread	Fever, Eosinophilia Lymphocytosis Lymphadenopathy Organ function abnormalities, as hepatitis, nephritis or other
FDE	Erythematous macule(s), plaque(s)	Solitary lesion(s)	Recurrence at the same sites by re-administration
GBFDE	Erythematous well-demarcated patches/plaques with blisters	Widespread lesions With large areas of uninvolved skin	Mucous membranes may be involved (not commonly) No systemic symptoms, patients are well
SJS/TEN*	Dusky red macules and flat atypical target lesions with blisters on top	Isolated lesions/confluence of lesions	Prodromal fever, upper respiratory tract symptoms Mucosal involvement Usually systemic symptoms Histology: subepidermal blisters, full thickness necrosis, immunofluorescence negative
AGEP	Pustules on oedematous erythema	Begins typically on face or intertriginous area, dissemination within hours	Fever Leucocytosis, neutrophilia, transient renal failure can occur Bacterial swab: sterile pustules
SDRIFE	Sharply delineated erythema	Flexural and intertriginous areas	Involvement of body folds; Usually no systemic involvement
Systemic photoallergic reactions	Dermatitis	Sun-exposed areas, may spread	Does not arise immediately on sun exposure (delay) Photopatch test

Legend: **GBFDE**-Generalized bullous fixed drug eruption; **SDRIFE**- symmetrical drug-related intertriginous and flexural exanthema. *Detachment **SJS** < 10%, **SJS/TEN overlap** 10%-30%, **TEN** > 30%.

1.2.3. Phenotypes and Endotypes

An inclusive definition of drug allergy to comprise phenotypes, endotypes, and biomarkers have emerged from a Practical Allergy Report (PRACTALL) document regarding a consensus precision medicine initiative between the European Academy of Allergy and Clinical Immunology (EAACI) and the American Academy of Asthma Allergy and Immunology (AAAAI) [18]. The purpose of this classification is a personalized approach based on disease endotypes, rather than phenotypes. It takes into consideration associated variations in genetic, pharmacologic, physiologic, biologic, and/or immunologic pathways within each phenotype [19].

Basically drug allergy is classified into different **phenotypes** according to the clinical characteristics and the timing of the reactions [18].

Immediate-onset DARs includes symptoms, such as urticaria/angioedema, respiratory, and/or gastrointestinal symptoms, and anaphylaxis within 1 to 6 hours of drug exposure. They are not limited to an underlying IgE-mediated mechanism. Two distinct presentations of IgE- mediated drug allergy reactions are considered (1) reactions after multiple doses of the drug, implying previous exposure to the drug and (2) reactions that occur after the first dose without previous exposure (e.g., reactions to cetuximab in patients previously sensitized to galactose-alpha-1,3-galactose, present on the humanized antibody) [20].

In **delayed-onset DARs** reactions usually occurs days to weeks after allergen exposure. These reactions have a great heterogeneity of clinical manifestations and can be subdivided in isolated single-organ involvement or systemic multiorgan involvement. Cutaneous reactions are the most common. Numerous clinical phenotypes exist according to the different clinical presentation as previously mentioned [18] (table 1 and 2).

Endotypes responsible for immediate and delayed DARs phenotypes include IgE-mediated endotype and non-IgE endotype involving direct mast cell direct activation, T-cell mediation, and genetic predisposition related to specific HLA-associated to drug reactions, among additional mechanisms [10,18] discussed ahead.

1.3 Physiopathology

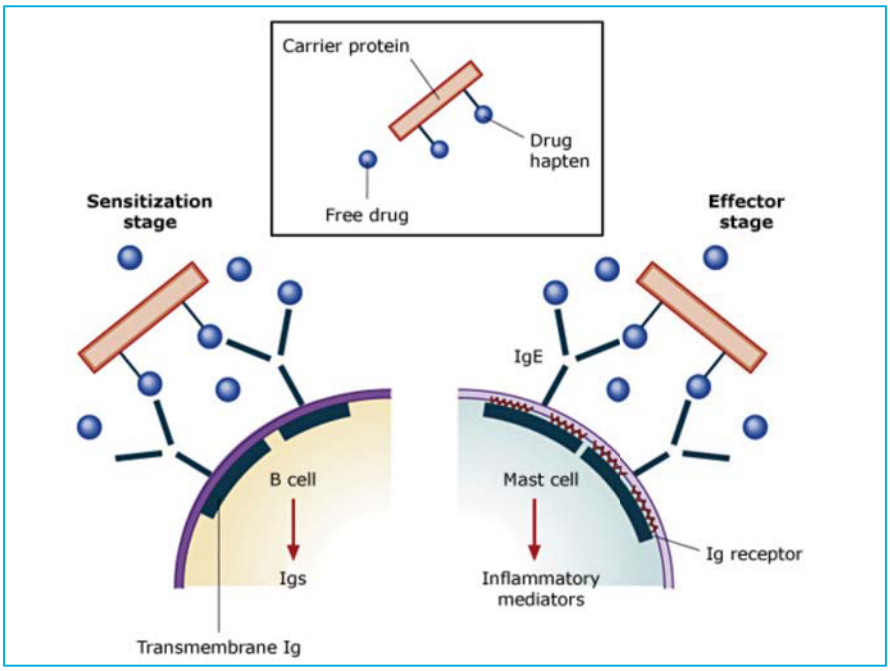
1.3.1. Immediate Reactions

A drug becomes an antigen able to elicit an immune response, through one of the two proposed mechanisms: 1. The drug, a chemically reactive small-weight molecule, must bind irreversibly to

a protein (**hapten concept**); 2. The drug chemically inert is first converted into reactive metabolites before binding irreversibly to a protein (**pro-hapten concept**).

IRs usually develop by an **IgE-mediate mechanism**, where specific-IgE (sIgE) are produced against a drug (hapten-carrier) during the sensitization phase (usually asymptomatic) and subsequently attaches to the high-affinity IgE receptors (FcεRI) on mast cell or basophils. On re-exposure the drug cross-links sIgE leading to mast cell activation and the release of several mediators and clinical symptoms. [2,21] (Figure 2).

Figure 3- **Type I, IgE-mediate drug reaction** (adapted from 22)



An alternative mechanism was recently described where specific drugs with the central tetrahydroisoquinoline (THIQ) motif such as neuromuscular blocking agents, fluoroquinolones and icatibant can activate directly activate mast cells through interaction with Mas-related G protein-coupled receptorX2 (MRGPRX2) and lead to an IR through a **non-IgE mechanism** [23].

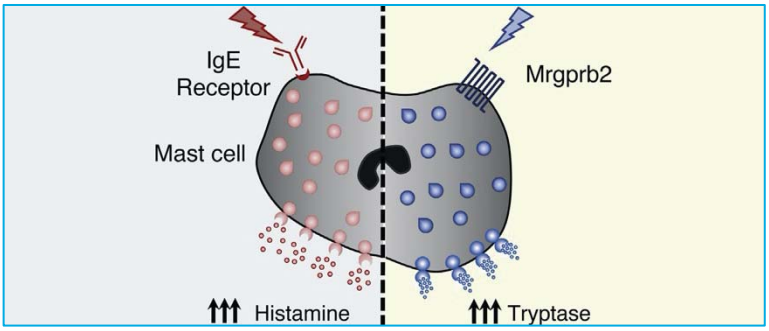


Figure 4- **Immediate reactions:**

IgE/non-IgE mediated: FcεRI/ MRGPRX2

1.3.2. Non-immediate reactions

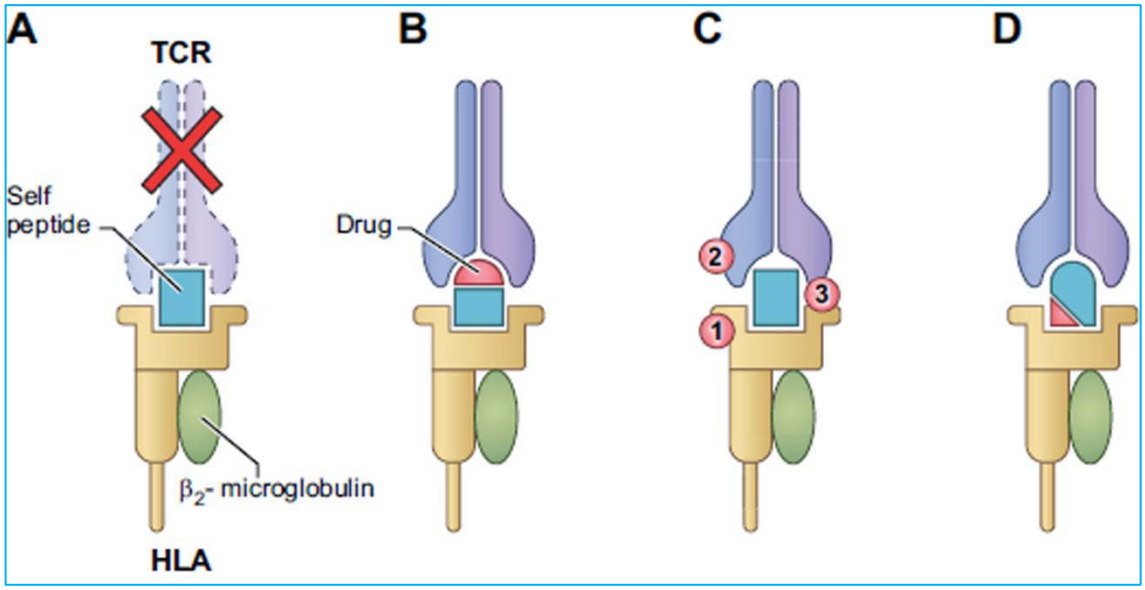
Most NIRs are mediated by T cells [2,20]. Cell-mediated immune reactions and activation of T cells are proposed to occur by three not mutually exclusive mechanisms [3,25] (Figure 5):

(1) The drug becomes an antigen ("**hapten/pro-hapten hypothesis**") and it is processed by antigen presenting cells. Then it can bind to human leukocyte antigens (HLA) and be presented to T-cell receptor (TCR). Activation of the innate immune system, namely dendritic cells, appears to be required [2,3,25];

(2) The "**pharmacological interaction with immune receptor concept" (p-i-concept**) states that the administered drug binds directly and reversibly to the immune receptor, either the TCR or HLA, resulting in T cell activation by pharmacological interaction. According to this hypothesis, the drug eliciting an immunological response is not dependent on its structural features nor metabolism. Chemically inert drugs are able to directly activate TCR [26];

(3) The "**altered-peptide repertoire hypothesis**" states that a low-molecular-weight drugs bind non-covalently to HLA class I molecules within the antigen binding cleft. This binding alters the shape of the antigen binding cleft and, as a result, alters the repertoire of peptides that are presented, including self-peptides. The individual is not necessarily tolerant to the new repertoire of peptides presented initiating a T-cell response [27].

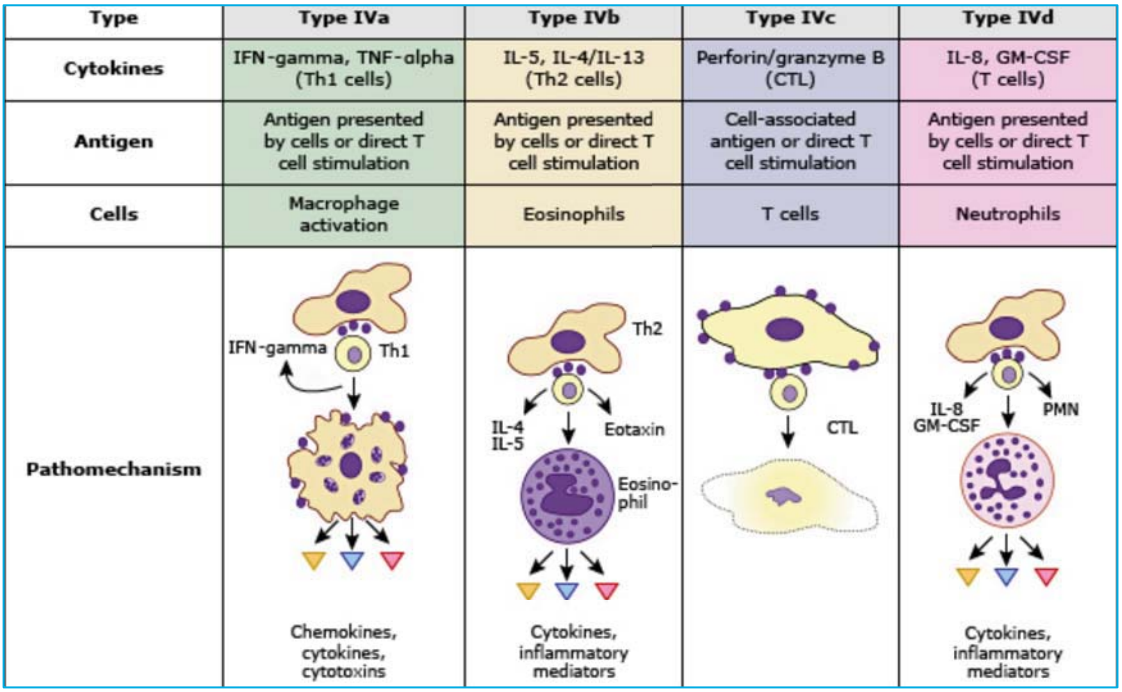
Figure 5. Mechanisms that mediate HLA or TCR associated drug hypersensitivity [3].



Legend: A. **Normal circumstances**(HLA bound self-peptides that bind with high affinity to a T cell-receptor resulting in the deletion of T cells bearing the auto-reactive receptor); **B**. **Pro-hapten/ Hapten hypothesis**; **C. Pharmacological Interaction hypothesis; D**. **Altered Peptide Repertoire hypothesis.**

Besides T cells, other immune cells are involved in NIRs, fitting into the **four subtypes of Type IV reactions** (Figure 5): I**Va**). Th1 cells produce interferon-γ activating macrophages, typically in eczema; **IVb)**. Th2 cytokines induce the production of antibodies by B cells and the eosinophil responses, mainly in MPE and DRESS; **IVc)**. CD4+ and CD8+ T cells produce cytotoxic mediators leading to keratinocyte apoptosis in MPE and massive apoptosis in SJS/TEN; **IVd)**. Production of CXCL8/IL8 by T-cells leading to neutrophil recruitment, mainly in AGEP [14].

Figure 6- T-cell mediated drug reactions- from Type IVa to Type IVd (adapted from 22)



In a minority of NIRs, other immune mechanisms may be involved. **Type II** reactions involve IgG-mediated cytotoxicity directed at membranes of erythrocytes, leukocytes and platelets. Drugs typically involved are methyldopa (hemolytic anemia), aminopyrine (leukopenia), and heparin (thrombocytopenia). These reactions occur only as long as the drug is present in soluble form. **Type III** reactions involve the formation of immune complexes (IC), a common event in a normal immune response, usually asymptomatic. On rare occasions, IC bind to endothelial cells and lead to IC deposition with complement activation in small blood vessels, resulting in serum sickness syndrome, drug-induced lupus erythematosus or vasculitis [21].

1.3.3. Pharmacogenetics

Associations between HLA haplotypes and specific drug reactions have been recognized for several years [18]. To generate an immune reaction, HLA molecules act as antigen presenters to immune T-cells. HLA class I (HLA A, HLA B, HLA C) molecules can be found on all nucleated cell surfaces and they present intracellular antigens to CD8+ cytotoxic T-cells [9].

In the field of drug allergy strong associations between severe reactions, mainly SCARs, and HLA-B alleles were found and represented a great achievement [18,28]. This led to a paradigm shift in the disease approach toward a personalized medicine, with screening for certain alleles recommended prior to specific drug therapy, particularly in high-risk populations [18,29]. The association between HLA-B*57:01 and abacavir hypersensitivity, a severe multi-organic disease [30], is a well-known example. The altered peptide repertoire model has been proposed to explain this reaction [27]. HLA-B*57:01 routine screening before abacavir use, according to strong evidence based guidelines, has drastically reduced reporting of abacavir hypersensitivity [29].

Strong associations between HLA- B*15:02 and the severe carbamazepine-induced SJS/TEN in Southeast Asian population induced screening programs in Southeast Asia and consequently reduced its prevalence [31]. HLA-B*15:02 screening before carbamazepine prescription in these high-risk populations was included in drug label. Associations between HLA-B*15:02 and oxcarbazepine-induced SJS/TEN are also well described and included on the drug label. Weaker associations between HLA-B*15:02 and SJS/TEN associated with other anticonvulsants such as phenytoin advise to risk-stratify patients before anticonvulsant prescription [29].

HLA-A*31:01 has been associated with several phenotypes of carbamazepine-associated T-cell–mediated reactions including MPE, DRESS, and SJS/TEN in Europeans, Japanese, and Koreans and provides helpful information in the prescription decision [29,32].

Other HLA relevant associations include HLA-B*5801 and allopurinol severe DARs. This association explains almost 100% of allopurinol- induced SJS/TEN and DRESS in Southeast Asians and approximately 60% in Europeans and other populations [29,33]. The carriage of HLA-B*5701 has been strongly associated with flucloxacillin-induced liver injury [28]; HLA-B*13:01 was associated to dapsone hypersensitivity in China; and HLA-A*32:01 with DRESS by vancomycin [29].

Recently, some polymorphisms in cytokine genes have been weakly associated with βL-induced anaphylaxis [34].

For phenytoin, the poor metabolizing genotype CYP2C9*3 has been associated with a wide spectrum of DARs including MPE, DRESS, and SJS/TEN, recommending dose reduction in those not carrying a high-risk HLA class I allele [29,31].

1.4. Diagnosis

An accurate diagnosis of drug allergy allows the accomplishment of the best measures for treatment and prevention. It is crucial to confirm the diagnosis and define safe alternatives for the allergic patient [2,10], but also to rule out the non-allergic cases and prevent the negative impact of an inappropriate drug allergy label [35].

The clinical evaluation of the patient with suspected drug allergy permitting a definitive diagnosis includes a thorough clinical history, standardized skin tests, reliable *in vitro* tests, and drug provocation tests and this is usually a time-consuming process [2].

1.4.1. Clinical history

As previously mentioned, drug allergy has a great heterogeneity of clinical presentations reflecting different underlying immunological mechanisms. A detailed and complete clinical history is essential for the proper diagnostic approach of the patient [2,10,36]. The use of a validated questionnaire like the drug hypersensitivity questionnaire developed by ENDA-European Network of Drug Allergy [37] is advisable and it allows the data to be recorded in a uniform format [2]. If the patient is observed during a symptomatic phase it also extremely important for the allergist to perform a physical examination [2,10].

1.4.2. Skin tests

The specific allergy diagnostic workup should only be carried out 4– 6 weeks after the complete resolution of all clinical symptoms and signs [2,10], as a potential mast cell mediator depletion that may temporarily lead to false-negative results after anaphylaxis [38]. There is evidence of desensitization of human skin mast cells and a minimum period of 4 to 7 days to restore full activating responses [39]. It is strongly recommended that trained staff and a proper setting to perform these specific procedures [2].

Skin prick tests (SPT) and **intradermal tests** (IDT) should follow standard procedures [40] and use validated concentrations [36,41]. Although, for several drugs the non-irritating concentrations are not available [10].

Skin tests are performed according to the DAR and the suspected mechanism involved. When the history suggests a potential IgE-mediated mechanism, SPT and ITD with immediate reading are recommended. In NIRs, when a T-cell mechanism is suspected, ITD with delayed reading (at 48 hours up to 96 hours, depending on the drug) should be considered [2,10,36,40,41]. **Patch test** could also be performed in these cases but standardized and validated test concentrations and vehicles are scarce for most drugs [2,36,41]. In the cases of severe NIRs as SCARs, skin tests

are contraindicated. Even patch testing is not recommended and the risk-benefit should be assessed [10].

The sensitivity and specificity of skin tests depend on the culprit drug and the potential mechanism but in many cases are not defined [2,10,18,36].

1.4.3. Drug provocation test

A drug provocation test (DPT) or drug challenge remains the gold standard for drug hypersensitivity. DPTs should only be performed under strictest surveillance conditions by trained staff and according to the recommendations and the contraindications [2,10,42]. Usually, they are subsequently performed in patients with negative skin tests if available and validated [2,10]. However, directed DPT is considered by some authors, particularly in children [43,44]. There is also a great diversity of protocols used for the procedure. There is no consensus in aspects such as number of steps [10] or the need for prolonged DTPs at home in NIRs [2].

1.4.4. *In vitro* tests

Specific in *vitro* tests can be particularly useful for severe life-threatening reactions when skin tests are negative or not available and DPT contraindicated, especially when multiple drugs are potentially implicated [2].

In *vitro* assay for **drug-specific IgE** is available for a limited number of allergenic drugs [10,45] but rarely have a critical role in patient evaluation [10]. The majority of these tests presents high specificity and a highly variable but usually low sensitivity, both depending on the drug assessed and the methods used [45].

Basophil activation tests (BAT) is based on flow cytometry and detects specific activation markers (commonly CD63 and CD203c) expressed on the surface of basophils after their incubation with the culprit drug or their metabolites [10,45]. It could be helpful in IRs, particularly in severe reactions, although it is not routinely available in clinical practice. Moreover, protocols are not standardized in terms of procedures and drug concentrations [45]. Specificity and sensitivity are under investigation for certain drugs, and further validation will require studies in larger sample populations [2,10].

The **lymphocyte transformation test** (LTT) is also not routinely available in clinical practice but it can be helpful in severe T-cell mediated reactions like SCARs [2]. Proliferation of drug-specific T cells upon stimulation with the suspected drug(s) is measured by the incorporation of [^{3}H] thymidine or 5,6-carboxyfluorescein diacetate succinimidyl ester content using flow cytometry.

[10,45]. These tests are not yet standardized and show a highly variable sensitivity and specificity, depending on the culprit drug and on the clinical manifestations [45].

General tests may be of interest during the symptomatic phase, namely a complete blood count with the differential focusing on eosinophil count, liver enzymes, and tryptase level [2,10].

Genotyping for the screening of patients at risk for SCARs with some drugs is crucial [10], as described above.

1.4.5. Biomarkers

In terms of precision medicine and drug allergy, several biomarkers were identified and are commonly used.

The most widely used *in vivo* biomarker for IgE-mediated reactions hypersensitivity reactions is immediate skin tests. Positive skin tests with validated concentrations are suggestive of drug-specific IgE.

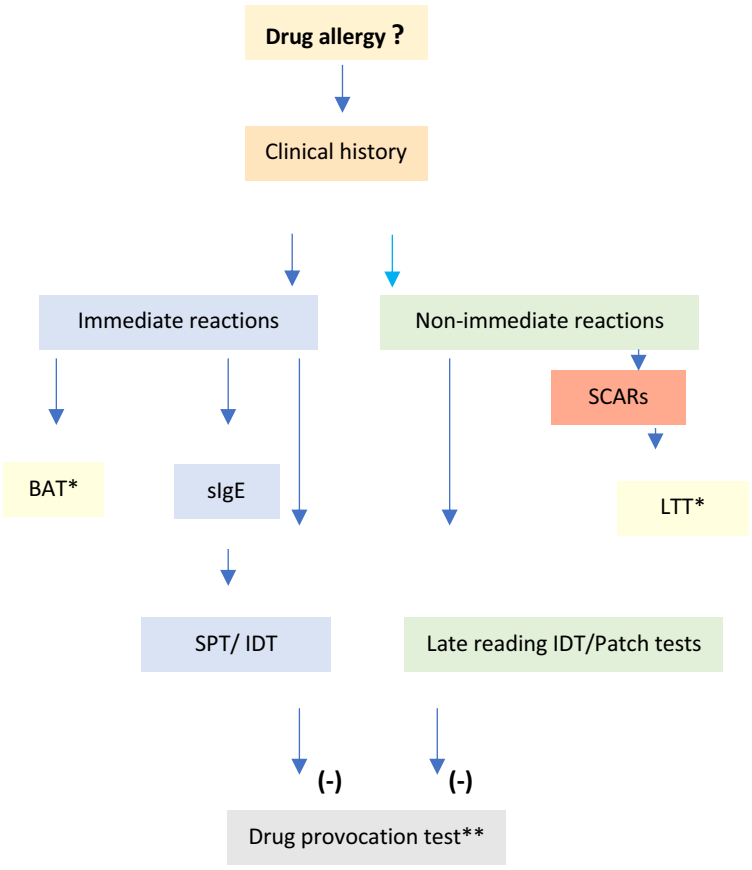
BAT and sIgE have also been used to provide evidence *in vitro* of IgE- sensitization. Tryptase is a mast cell protease released during cell activation and its blood levels correlate with the extent of the reaction, with patients presenting higher levels during an anaphylactic reaction to drugs [10,18].

Some potential biomarkers of T cell-mediated drug reactions were identified as LTT and the skin tests described above.

Markers of inflammation such as granzyme B and granulysin have been identified in SCARs such as SJS/TEN [18]. A recent report refers that granulysin expression in $CD3^{+}CD4^{+}$ T cells, in association with granzyme B and IFN-c expression, may provide a high sensitivity and specificity for patients with SJS/TEN [46]. Moreover, granulysin concentrations in blister fluid seem to correlate with the severity of SJS/TEN [47] and high granulysin serum levels may be a useful and early diagnostic biomarker[48].

1.4.6. Drug allergy diagnostic work-up

Figure 7- Algorithm for drug allergy diagnostic work-up (based on 2 and 45)



* In severe reactions and/or for high-risk patients;

Consider also performing for drugs that skin tests are not available and/or for patients that skin tests are not feasible;

2. Risk factors for drug allergy

Some factors have been associated with an increased risk of developing drug allergy, with the clinical expression and the severity of the DARs. They include patient-related factors and drug-related factors [1,9,21,49].

A deeper understanding of risk factors for drug allergy is crucial, given the potential severity of these reactions, even life-threatening [2]. Research on identification of subjects at high risk will certainly be intensified in the near future with a focus on a personalized medicine [49].

2.1. Drug-related risk factors

Drug-related factors that determine its immunogenicity include a large-molecular weight, ability to act as a hapten, a pro-hapten or to covalently bind to immune receptors (p-i concept) [9,49]. For this reason along with consumption patterns, certain classes of drugs, namely ßL, sulfonamide antibiotics, antiepileptics and also NSAIDs, tend to be associated with a higher frequency of DARs compared with other classes [4,9,14,49,50].

Other factors that appear to increase the risk of drug sensitization are the route of administration (topical and parenteral vs oral), the duration of treatment (prolonged high doses administration vs large single dose), and the frequency of exposure (intermittent or repeated administration vs uninterrupted treatment) but controlled studies to support these findings are needed [1,9,21,49,51].

Treatment with multiple drugs seems to increase the risk of reaction although the exact mechanism is not fully understood. Excessive demands on enzyme systems oxidation or acetylation of multiple drugs may interfere with metabolism, leading to accumulation of reactive metabolites and drug interactions [49, 51].

2.2. Patient-related risk factors

Patient-related risk factors for drug allergy include demographic factors, genetic factors, and certain disease states [1,2,9,10,35,49].

2.2.1. Demographic factors

Females have a higher risk for DARs but the reasons are not well-defined [9,10,35,49]. The risk is higher for both immediate and non-immediate reactions [52]. Gender-related differences in pharmacokinetic, pharmacodynamic, hormonal, and immunological factors as well as differences in the medication consumption patterns were suggested as possible explanations [53]. Although higher rates of DARs reported among female hospitalized patients, no significant differences were found between both sexes regarding clinical manifestations and mortality [54]. At paediatric ages, the female gender does not appear to be a risk factor for DARs [9,49,55].

Age is not known to be an independent risk factor for drug allergy [52].

2.2.2. Atopy and allergic diseases

Atopic patients or patient with allergic diseases are not known to be at increased risk for drug allergy [9,44,49,56], but these conditions may predispose to more severe IgE-mediated DARs [57].

Although, a recent study involving adult patients with immediate DARs to ßL antibiotics reported that several parameters of atopy were predictors of these type of reactions [58].

2.2.3. Personal history of drug allergy

A previous history of DARs obviously increases the risk of further reactions to the same drug or to cross-reactive drugs [9,49,55,56].

The multiple drug allergy syndrome describe patients with immunologic reactions to at least two or more chemically unrelated drugs. It may include both immediate and non-immediate reactions although higher rates are described among patients with IgE-mediated reactions [9,10,49, 59,60]. In patients with DRESS the introduction of another drug may induce the relapse of the reaction and/or additional sensitization to newly introduced drugs, previously well tolerated [49, 59, 60].

2.2.4. Concomitant disease

Some DARs have higher probability to occur among patients with particular concomitant disease state [9,10,35,49] since these can create an inflammatory milieu that enhances drug allergy or produce changes in metabolic pathways. Patients with HIV infection have very high rates of DARs to sulfonamides and other drugs [9].

Various viral infections act as co-factors and cause immune stimulation predisposing to DARs. Mild skin reactions associated to the Epstein-Barr virus (EBV) infection are frequent in children treated with aminopenicillins [2]. Similarly, reactivation of some herpes virus appears to be associated with the pathogenesis of DRESS [2, 9, 28].

Patients with cystic fibrosis (CF) are likely at higher risk of drug allergy namely to antibiotics, probably due to the increased use of high-dose of intravenous antibiotics [9,10,35]. Although, these data are mainly based on clinical history [49].

2.2.5. Genetic factors

Knowing some genetic factors that predispose to certain types of DARs in susceptible population was a huge achievement in the field of drug allergy, as described above.

Table 3- Pharmacogenomic biomarkers in drug allergy (based on 9, 29, 36 and 49).

Class of Drug	Drug	Genetic Association	Clinical Phenotype	Population
Antiepileptic drugs	Carbamazepine	HLA- B*15:02 HLA- B*15:21	SJS/TEN	Han Chinese, Malaysian, Hindu Indian
	Carbamazepine	HLA- B*15:11	SJS/TEN	Korean, Japanese
	Carbamazepine	HLA- B*15:18 HLA- B*59:01	SJS/TEN	Japanese
	Carbamazepine	HLA- A*31:01	SJS/TEN	Northern European, Japanese, Korean
	Carbamazepine	HLA- A*31:01	DRESS/MPE	European, Japanese, Chinese
	Oxcarbazepine	HLA- B*15:02 HLA- B*15:18	SJS/TEN	Han Chinese
	Phenytoin	HLA- B*15:02	SJS/TEN	Han Chinese, Thai
	Phenytoin	HLA- B*13:01 HLA- C*08:01/DRB1*16:02	SJS/TEN	Han Chinese
	Phenytoin	CYP2C9*3	SJS/TEN/DRESS	Taiwanese, Japanese, Malaysian
	Phenobarbital	?HLA- B*51:01	SJS/TEN	Japanese
	Lamotrigine	HLA- B*51:02 HLA- B*38 HLA- A*68:01	SJS/TEN	Han Chinese
	Zonisamide	?HLA- A*02:07	SJS/TEN	Japanese
Antiretroviral drugs	Abacavir	HLA- B*57:01	Hypersensitivity Reaction	Caucasian
	Nevirapine	HLA- B*35:05	Rash	Thai
	Nevirapine	HLA- C*04	Rash	African, Asian, European
	Nevirapine	HLA- B*57:01	Rash	Thai
	Nevirapine	HLA- DRB1*01	Rash	French
	Nevirapine	HLA- B*14/ C*08	DRESS	Sardinian/Japanese
	Nevirapine	HLA- B*35/ C*04	DRESS	SE Asian

	Nevirapine	HLA- C*04 + CYP2B6 G --> T	DRESS	European, Asian, African
	Nevirapine	HLA- B*35:01	DRESS	Thai/European
	Nevirapine	CYP2B6 G --> T HLA- C*04:01 CYP2B6 T --> C	SJS/TEN	African/Malawian Mozambican
	Nevirapine	HLA- DRB1*01:01	Hepatitis	European
	Nevirapine	HLA- DRB1*02:01 HLA- B*58:01	Hepatitis	South African
	Efavirenz	HLA- DRB1*01:01	Rash	French
	Raltegravir	HLA- B*53:01	Pruritis, diaphoresis, rash	African ancestry
Xanthine oxidase inhibitor drugs	Alopurinol	HLA- B*58:01	SJS/TEN	Han Chinese, Taiwanese Thai, Japanese, European
Antibiotic drugs	Dapsone	HLA-B*13:01	Hypersensitivity	Chinese
	Flucloxacillin	HLA-B*5701	Hepatitis	
	Vancomycin	HLA-A*32:01	DRESS	
	Penicillin	E237G variant of FceR1b gene, IL-4RaQ576R polymorphism, IL-4 Il-13-SNP polymorphisms	Type I reactions	Chinese
	ßL antibiotics	Il-13 (R130Q, -1055C > T variants) and IL-4RA (150V, S478P, Q551R variants) polymorphisms	Type I reactions	Italians
	ßL antibiotics	Ile75Val variant of IL-4Ra gene two linked Il-10 promotor gene polymorphisms (-819C > T and -592C > A)	Type I reactions	Caucasians
	Antituberculosis Drugs	CYP2E1 in the Chinese	Hepatitis	Chinese
		NAT2 genotype	Hepatitis	Korean
		GST genotype	Hepatitis	Caucasian
NSAID	Metamizole	CYP2C9, CYP2C19, NAT2 genotypes	Anaphylaxis	

Legend: **CYP –** cytochrome **P450; FceR1b** -high affinity IgE receptor b chain; **NAT2-**N- acetyltransferase2, **GST-** glutathione- S-transferase.

2.3. Drug allergy in the overall context of allergic diseases

2.3.1. Inflammatory and metabolic factors

The incidence of allergic diseases has increased greatly over the past decades, especially in developed countries and some factors of a westernized lifestyle have emerged as potential contributors, including obesity and changes in dietary pattern [61].

In fact, the incidence of allergic diseases increased in parallel with obesity [62, 63] and several studies linked these two diseases. Most studies involved asthmatic patients [64-71], but also patients with allergic rhinitis [72-76] and atopy [63,77,78]. Some hypotheses were advanced in order to explain this potential association [62, 64,76,79, 80] but further investigation is needed. However, it is established that much of the obesity risk is related to the persistent low-grade systemic inflammation [81- 85] that can be modulated by diet [86-89]. Research on asthma and other allergic diseases suggest that diet may influence susceptibility to allergic diseases as it contributes to the immune system regulation [61].

There are no published studies involving patients with drug allergy.

2.3.2. Psychological markers

The potential relevance of personality factors in clinical manifestations of allergic diseases has been under investigation for a long time but is still a matter of debate [90]. Several studies demonstrated an important association between allergic diseases and the psychological characteristics of patients, namely in skin and respiratory allergic diseases [90-94]. Only a few studies have evaluated the psychological profile of patients with drug allergy but these patients appear to have more psychological disturbances than those with asthma or rhinitis [94].

3. Impact of drug allergy on patients quality of life

A better and a complete approach of patients should also include patient-reported outcomes (PROs) evaluation. PROs concern all health-related reports coming exclusively from the patient, without involvement of interpretation by physicians or others [95]. Recently, PROs have gained relevance in clinical practice, research and regulatory processes, as they allow a better understanding of patients subjective assessment of their health condition [95].

Clinical practice suggests that drug allergy has an intense emotional content from the patient's perspective. Due to its unpredictable nature and potential severity, patients experience emotions such as anxiety, fear, and tension related to drug intake, disease management, and present/future health problems [96]. However, the evaluation of the impact of drug allergy on patient´s quality of life has been rarely explored, particularly in the Portuguese population.

II. AIM

The aim of this investigation presented in this thesis was to investigate whether individual factors such as demographic, psychological characteristics, metabolic and/or inflammatory factors are associated with a higher susceptibility to drug allergy.

For this purpose, 3 objectives were defined and separated by chapters as follow:

Chapter 1 – Overview of Drug Allergy

- To evaluate the evidence available in the field of drug allergy through a narrative review on pathophysiology, clinical presentation, classification, risk factors and the drugs most frequently involved (study 1).

Chapter 2 – Risk factors and other markers in Drug Allergy

- To characterize βL antibiotic allergy in a paediatric population, investigating potential risk factors (study 2);
- To assess differences in the psychological characteristics of patients with suspected drug allergy in comparison with healthy controls (study 3);
- To investigate a potential link between drug allergy and obesity (study 4);
- To assess a potential association between dietary parameters and drug allergy (study 5).

Chapter 3 – Impact of Drug Allergy on the patient

- To translate and cross-cultural validate the original version of the Drug Hypersensitivity Quality of Life Questionnaire to the Portuguese population and to determine the impact of drug hypersensitivity on patient´s health-related quality of life (study 6).

III. CHAPTER 1

Overview of Drug Allergy

Study I - “Overview of Drug Allergy: From Immunogenetics to Practice”

Acta Med Por 2018 Oct; 31(10):581-588

Overview of Drug Allergy: From Immunogenetic Basis to Practice

Alergia a Fármacos: Da Imunogenética à Clínica

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Acta Med Port 2018 Oct;31(10):581-588 ▪ https://doi.org/10.20344/amp.10092

ABSTRACT

Drug therapy is often a balance between the beneficial and harmful effects of drugs. Drug allergic reactions are adverse reactions mediated by immunological mechanisms and usually not related to the pharmacological actions of the drug. They can be classified based either on the clinical presentation or the underlying immunological mechanism. Although uncommon, drug allergic reactions are unpredictable and can be very severe, even life threatening. The aim of this review was to provide clinicians from different medical specialties with a working tool to improve management of their patients with suspected drug allergy. It was conducted as a non-systematic review, and attempts to describe the complexity of drug allergy. The information included ranges from pathophysiology to the heterogeneous clinical presentation, with a special focus on the drugs most frequently involved, as well as a classification of reactions and risk factors. Despite all advances in this challenging and complex field of allergy and clinical immunology, drug allergy is not yet fully established and understood. An exceptional contribution was brought by pharmacogenomics, even though a specific pharmacogenetic association has only been defined for a very limited number of drugs. Further studies are needed to obtain clearer answers when managing each individual case of drug allergy.

Keywords: Drug Hypersensitivity/etiology; Drug Hypersensitivity/immunology; Pharmacogenetics; Drug-Related Side Effects and Adverse Reactions

RESUMO

A terapêutica farmacológica consiste, frequentemente, num equilíbrio entre os efeitos benéficos e prejudiciais dos fármacos. As reações alérgicas a fármacos são reações adversas mediadas por mecanismos imunológicos e não relacionadas com as ações farmacológicas do fármaco. Podem ser classificadas quer com base na apresentação clínica, quer no mecanismo imunológico subjacente. Embora pouco comuns, as reações alérgicas a fármacos são imprevisíveis, podendo ser graves e potencialmente fatais. O objetivo da presente revisão da literatura foi disponibilizar aos clínicos de diversas áreas médicas uma ferramenta de trabalho para uma melhor abordagem dos seus doentes com suspeita de alergia a fármacos. Foi conduzida de forma não sistemática e procura descrever a complexidade das reações alérgicas a fármacos, desde a fisiopatologia à heterogeneidade da apresentação clínica. Foi dado especial destaque aos fármacos mais frequentemente envolvidos, à classificação das reações e aos fatores de risco. Apesar de todos os avanços nesta área desafiante e complexa da alergologia e imunologia clínica, a alergia a fármacos não está ainda completamente compreendida e estabelecida. A farmacogenética trouxe um contributo excecional, embora apenas para um número muito limitado de fármacos esteja definida uma associação farmacogenética. São necessários estudos adicionais que permitam obter respostas mais diretas na abordagem de cada caso individual de alergia a fármacos.

Palavras-chave: Efeitos Colaterais e Reações Adversas Relacionados a Medicamentos; Farmacogenética; Hipersensibilidade a Medicamentos/etiologia; Hipersensibilidade a Medicamentos/imunologia

INTRODUCTION

Drug therapy is often a balance between the beneficial and harmful effects of drugs. Despite the intensive research in the field, adverse drug reactions (ADRs) remain a major problem. An ADR has been defined by the World Health Organization as any noxious, unintended and undesired effect of a drug occurring at doses normally used for prevention, diagnosis or treatment.[1] It has been estimated that ADRs account for 3% to 6% of all hospital admissions and occur in 10% to 15% of hospitalized patients, contributing to morbidity and mortality.[2,3] A widely used classification system divides ADRs in type A (predictable, common, related to the pharmacological properties of the drug), and type B (unpredictable, uncommon, unrelated to the pharmacological actions of the drug). The first type comprises approximately 80% of all ADRs and includes drug-induced toxicity, side effects and drug interactions.[4-7] Drug allergic reactions (DARs) are those mediated by immunological mechanisms and belong to type B. In practice, based on the clinical presentation alone, it is often difficult to differentiate between immune and non-immune mediated reactions. Therefore, the term drug hypersensitivity is applied when an immunological mechanism cannot be demonstrated in drug reactions that clinically look like allergic. Drug hypersensitivity reactions (DHRs) comprise 15% of all ADR. DARs, although less common (estimated to represent a small percentage of all ADRs), can be very complex and potentially severe, even life-threatening.[1,4]

The study of DARs is challenging[5] and is constantly updated as new drugs are developed and drug consumption patterns are changed.[6]

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The aim of this review of the current literature was to provide clinicians from different medical specialties with a working tool to improve management of their patients with suspected drug allergy (DA). It was conducted as a non-systematic review, and attempts to describe the complexity of DA. The information included ranges from pathophysiology to clinical presentation, with a special focus on the drugs most frequently involved, as well as classification of reactions and risk factors.

1 – Classification

A consensus classification is mandatory to guide and validate the diagnostic work-up. DARs can be classified based on the clinical presentation or the underlying immunological mechanism (Table 1).

Clinically, DARs are classified depending on the time elapsed between drug administration and the onset of symptoms: immediate (usually occurring up to one hour; could be between 1 to 6 hours: accelerated reactions) and non-immediate (at any time, after one hour and up to several days of drug administration).[4]

Any of the four immunologic mechanisms proposed by Gell and Coombs may underlie DARs, being the IgE and T-cell-mediated the most common.[4,9] Type I, also known as immediate reactions (IRs), are mediated by drug-specific IgE antibodies. Type II (cytotoxic) and Type III (immune complex) are mediated by drug-specific IgG or IgM antibodies. Type IV are mediated primarily by T cells[4-6,9-12] and have been recently classified in 4 subtypes, according to cytokine patterns and the preferential activation of different immunocytes.[9]

2 – Clinical Presentation

2.1 – Immediate reactions (IRs): IRs present as isolated symptoms (urticaria, angioedema, conjunctivitis, rhinitis, bronchospasm) or as a severe reaction such as anaphylaxis. Urticaria/angioedema and anaphylaxis are the most common. The IgE-mediated allergy to β-Lactam (βL) antibiotics is the paradigmatic example.[4,13,14]

2.2 – Non-immediate reactions (NIRs): The skin is the most frequently involved organ, with a wide range of clinical presentations. Maculopapular exanthema (MPE) and delayed urticaria are the most common.[4,6,10,13] Fixed drug eruption (FDE), acute generalized exanthematic pustulosis (AGEP), erythema multiforme (EM) and eczema are other presentations.[12]

Both skin and other organs can be involved, as in drug rash with eosinophilia and systemic symptoms (DRESS)/ drug-induced hypersensitivity syndrome (DiHS), vasculitis and Stevens-Johnson syndrome (SJS)/ toxic epidermal necrolysis (TEN).[4,6,10,13.]

Mild eruptions usually occur one to few days after the drug treatment is started, while most severe reactions often

Table 1 - Classification of drug allergies (adapted from [4])

Type	Type of immune response	Pathophysiology	Timing of reaction	Clinical symptoms	Typical chronology of the reaction
I	IgE	Mast cell and basophil degranulation	Immediate	Anaphylaxis Urticaria/Angioedema Bronchospasm Rhinitis	Immediate, usually up to one hour, but could occur between 1h to 6h after the last drug intake
II	IgG and complement	IgG and complement-dependent cytotoxicity	Non-immediate	Cytopenia	5 – 15 days after the start of the eliciting drug
III	IgM or IgG and complement or FcR	Deposition of immune complexes		Serum sickness Urticaria Vasculitis	7 – 8 days after the start of the eliciting drug for serum sickness/ urticaria; 7 – 21 days for vasculitis
IV a	Th1 (IFN-gamma)	Monocytic inflammation		Eczema	1 – 21 days after the start of the eliciting drug
IV b	Th2 (IL-4 and IL-5)	Eosinophilic inflammation		MPE DRESS/ DiHS	1 to several days after the start of the eliciting drug for MPE; 2 – 6 weeks for DRESS/DiHS
IV c	Cytotoxic T cells (perforin, granzyme B, FasL, granulysin)	Keratinocytic death mediated by CD4 or CD8		MPE FDE SJS/TEN	1 – 2 days after the start of the eliciting drug for FDE; 4 – 28 days for SJS/TEN
IV d	T cells (IL-8/CXCL8)	Neutrophilic Inflammation		AGEP	1 –2 days after the start of the elicitting drug, but can be longer

IgE: Immunoglobulin E; IgM: Immunoglobulin M; IgG: Immunoglobulin G; Th1: T helper1; Th2: T helper 2; IFN gamma: Interferon gamma; IL4: Interleukin 4; IL5: Interleukin 5; IL8: Interleukin 8; CXCL8: Chemokine motif ligand 8; MPE: Maculopapular exanthema; DRESS: Drug rash with eosinophilia and systemic symptoms; DiHS: Drug-induced hypersensitivity syndrome; FDE: Fixed drug eruption; SJS: Stevens-Johnson syndrome; TEN: Toxic epidermal necrolysis; AGEP: Acute generalized exanthematic pustulosis.

begin later on (SJS/TEN: 4 - 21 days; DRESS/DiHS: 2 - 6 weeks).[4]

DRESS is an unusual DAR characterized by the presence of morbilliform rash, atypical lymphocytosis, eosinophilia, fever and other organ involvement, usually liver.[12,15] A minimum criterion of rash, fever, hepatitis and lymphocytosis has been proposed for DiHS.[16]

SJS and TEN, the most severe type of reactions affecting the skin, are characterized by extensive epidermal detachment and mucous membrane erosion, including oral, conjunctival and anal.[10,12] Although uncommon (estimated prevalence: 5 - 6 cases and 1 - 2 cases per million patients for SJS and TEN, respectively),[17] the morbidity and mortality is high (5% - 10% mortality for SJS[16,17] and 30% - 50% for TEN).[12,16-18] Several authors support that SJS and TEN are a single disease with common causes and physiopathology, but different spectrums of severity according to the extension of epidermal detachment (< 10% : SJS; 10% – 30% : SJS – TEN overlapping; > 30% : TEN).[10,12,16-18] Drugs causing SJS/TEN overlap with those causing DRESS/DiHS: aromatic amine anticonvulsants, sulfonamides antibiotics, nonsteroidal anti-inflammatory drug (NSAIDs) and antiretroviral agents. Allopurinol and lamotrigine were also associated with SJS/TEN.[10,12,16,17]

EM is characterized by the presence of target-shaped lesions and, although less severe, can be an early presentation of SJS/TEN. Any of these reactions contraindicate the re-administration of the culprit drug.[12]

3 – Pathogenesis and Physiopathology

3.1 – Chemical basis: For a drug to become an antigen able to elicit an immune response, two main mechanisms have been proposed: 1. The drug, a chemically reactive small-molecule, must bind irreversibly to a protein, generating antigens (hapten concept); 2. The drug, chemically inert, needs to be converted into reactive metabolites before binding irreversibly to proteins (pro-hapten concept).[4-5,19-22]

For T-cell mediated reactions, the role of a carrier-protein/hapten has not been fully defined as it has been for IgE-mediated reactions.[4,19]

An alternative hypothesis is that some drugs might also originate a direct reversible interaction with the T-cell receptors or HLA-molecules, activating T cells by pharmacological interaction (p-i concept).[9] According to this hypothesis, the drug eliciting an immunological response is not dependent on its structural features nor metabolism. Chemically inert drugs are able to directly activate T-cell receptors.[4-5,11,20,21]

Cross-reactivity between drugs is an immunological reaction that occurs on exposure to different drugs with a similar molecular structure. This can happen even without any previous exposure to the cross-reacting drug, allowing to predict, to some extent, the risk of reactivity to chemically related drugs.[11]

3.2 – Immunopathological mechanisms: It has been proposed that drug-protein conjugates might be processed and presented by antigen-presenting cells to naive T cells, after drug intake, inducing tolerance or effector responses.[24] In the last case, the immune system develops either immediate T-helper2 (Th2)- type responses, mediated by specific IgE antibodies, or non-immediate Th1-type responses, mainly mediated by specific T cells.[5,10] Alternatively, T cells could be directly stimulated by the drug.[9]

3.2.1 – Immediate reactions: IRs develop as a result of IgE production. At an initial sensitization phase, B-cells proliferate and differentiate into plasma cells, in the presence of specific Th2-cells. Drug-specific IgE are then produced and bind to the high-affinity FcRI receptors on the surface of mast cells and basophils. On subsequent drug exposure, the drug antigen cross-links IgE on the surface of mast cells, activating them and inducing the release of preformed mediators (e.g., histamine, tryptase, TNF-α) and the production of new ones (e.g., leukotrienes, prostaglandins, cytokines). The sensitization phase is usually asymptomatic and may have occurred during an earlier drug treatment.[4,5]

3.2.2 - Non-immediate reactions: The majority are mediated by T lymphocytes.[4] Most of the information available relates to the specific effector immune response mediated by T cells. Little is known about the initial steps mediated by the innate immune system, mainly by dendritic cells.[10,23] It has been proposed that these cells can process the drug antigen as a first step to stimulate naive T cells.[4] The antigen is internalized and transported to the regional lymph nodes, where it is presented to naive T cells. Alternatively, it may stimulate directly pathogen-specific T cells, without priming by dendritic cells. Antigen-specific T cells migrate to target organs and on re-exposure to the drug, are activated to secrete cytokines.

Other immune cells are involved in NIRs, fitting into the four subtypes of Type IV reactions[9]: IVa). Th1 cells produce interferon-γ-activated macrophages, typically in eczema; IVb). Th2 cytokines induce the production of antibodies by B cells and the eosinophil responses, mainly in MPE and DRESS; IVc). CD4+ and CD8+ T cells produce cytotoxic mediators leading to keratinocyte apoptosis in MPE and massive apoptosis in SJS/TEN; IVd). neutrophil recruitment and T-cell-induced activation by the production of a chemokine, CXCL8, mainly in AGEP.

The histopathology findings in SJS/TEN show detachment of a large portion of the epidermis.[12] Previously, Fas-FasL interaction and perforin-granzyme B were the pathways reported as basic effectors.[12,16] More recently, granulysin was described as a key effector responsible for the death of keratinocytes.[16,18,24] Granulysin concentrations in blister fluid seem to correlate with the severity of SJS/TEN[24] and high granulysin serum levels may be a useful early diagnostic biomarker.[18]

In a minority of NIRs other immune mechanisms may be involved. Type II reactions concern IgG-mediated cytotoxicity directed to membranes of erythrocytes, leukocytes and platelets. Drugs typically involved are methyldopa (hemolytic anemia), aminopyrine (leukopenia), and heparin (thrombocytopenia). Such reactions may occur only as long as the drug is present in soluble form. Type III reactions

involve the formation of immune complexes (IC), a common event in a normal immune response, usually asymptomatic. On rare occasions, IC bind to endothelial cells and lead to IC deposition with complement activation in small blood vessels, resulting in serum sickness syndrome (SSS), drug-induced lupus erythematosus or vasculitis.[5]

3.3 – Pharmacogenetics: The discovery of strong associations between certain severe reactions, mostly NIRs, and HLA-B alleles has allowed a great progress in DA.[4,16-18,20,21] The association of HLA alleles with SJS/TEN has been reported, for the first time, more than 25 years ago.[25] Since then, specific HLA alleles have been found to be associated with this disease.[17] A strong association between carbamazepine (CBZ)-induced SJS/TEN and HLA-B*1502 has been described in a Chinese population, where this allele was present in all patients suffering from CBZ-induced SJS. Subsequently this association was also found in Indian and Thai, but not in Japanese nor in European patients.[16,21] This association seems to be phenotype-specific (SJS/TEN)[4] and is stronger than any other described so far.[17,21]

In northern Europeans, the presence of HLA-A*3101 has been associated with a wide spectrum of CBZ-induced reactions (MPE, DRESS/DiHS, SJS/TEN).[26]

Other important association include HLA-B*5801 and SJS/TEN or DRESS/DiHS with allopurinol, in Asian[16] and European populations.[16,27]

Finally, the carriage of HLA-B*5701 has been strongly associated with flucloxacillin-induced liver injury[16,21] and with abacavir hypersensitivity syndrome, a severe multi-organic reaction.[16,21,28,29] This association was higher among Caucasians, where the allele was present in 94.4% cases (positive predictive value ≥ 70%; negative predictive value: 95% - 98%).[29] International HIV treatment guidelines recommend the HLA-B*5701 screening prior to the abacavir treatment.[30]

Recent pharmacogenomic studies evolving from a candidate-gene approach to the genome-wide association study (GWAS) brought great advances in the discovery of genes associated with inter-individual differences in drug response (mainly genes predisposing to ADRs but also genes responsible for drug efficacy). The HLA system has been a major focus for type B reactions, particularly the more severe immune reactions.[16,17] A number of polymorphisms located on chromosome 6 have been found in association with SJS/TEN induced by allopurinol[31] and abacavir.[32] In IRs, some polymorphisms in cytokine genes have been weakly associated with βL-induced anaphylaxis.[33-35]

This greater knowledge has made some DARs quite predictable.[16,20,21]

3.4 – Risk factors: There are few identified factors influencing the risk of sensitization and the severity of DARs. These are the chemical structure of the molecule, the nature of drug exposure (dose, route, frequency and duration), the presence of co-factors (e.g. stress, infections), genetic predisposition, immune status and female gender.[1,5,20] In the balance between drug and individual factors (Fig. 1), a disturbed immunologic status associated with the development of recurrent infections, decreases the threshold to induce a response. Moreover, the HLA genotype can dictate the way in which a drug can cause allergy.[22]

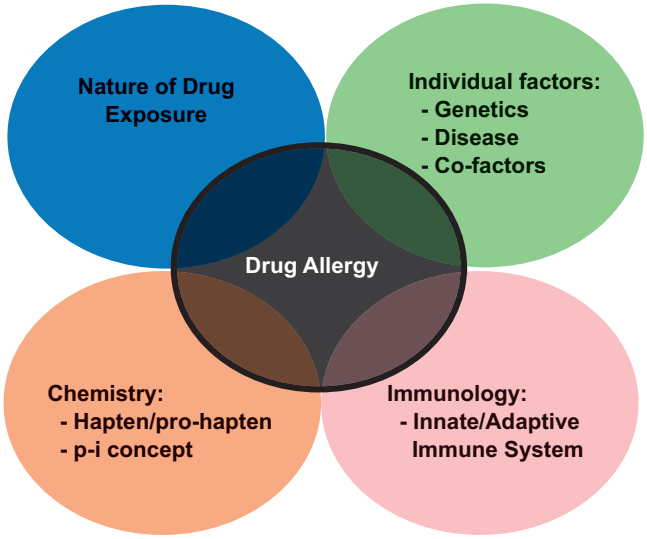

Figure 1 – Drug Allergy: a balance between drug factors and patient biology (adapted from [21])
p-i concept: Pharmacological interaction with immune receptors.

Anaphylaxis has been associated with certain drugs (NSAIDs, radiocontrast media, antibiotics, opioids, perioperative drugs) in patients with mast cell disorders. However, data are scarce and evidence for an association is limited. Nevertheless, mastocytosis should be ruled out in cases of severe anaphylaxis.[36]

3.4.1 – The role of viruses: Viral infections are the main cause of skin reactions that can mimic DARs if the drug, usually an antibiotic, is taken simultaneously. Viruses can also interact with drugs and immune system, leading to allergic reactions such as the mild ampicillin exanthema linked to the Epstein-Barr virus (EBV) infection or DRESS/DiHS.[4,10,20-22,37,38] DRESS/DiHS is the best studied DAR associated with viral infection and has been linked to the reactivation of human herpes virus (HHV)-6. EBV, cytomegalovirus and other HHV, even days or weeks after the discontinuation of the drug.[4,10,16,22,38,39]

The interaction with the immune system can occur at several points: drug metabolism; drug presentation to T cells, by dendritic cells; and effector response (cytokine and chemokine production).[10]

4 – Allergic reactions to specific drugs

4.1 – Antibiotics

4.1.1 – β-Lactams: βLs are still the most frequent cause of DARs. Benzylpenicillin was the first βL implicated, but amoxicillin has progressively become the most common culprit. A wide range of manifestations can occur, reflecting different underlying immunological mechanisms. They can induce IRs, mediated by IgE (usually urticaria/angioedema and anaphylaxis) and also NIRs (mainly MPE). Severe NIRs (AGEP, SJS/TEN, DRESS) can also occur.[6,13]

βLs clearly induce immunological reactions due to hapten-carrier formation which occur through the nucleophilic opening of the βL ring and the generation of reactive intermediates.[6,13,22] Recent studies have pointed out the relevance of the three-dimensional shape of the βL, as well as its inherent chemical reactivity, in determining the selectivity of the covalent binding.[20] The role of side chains that distinguish different penicillin compounds as relevant allergenic determinants is also widely accepted, particularly in IRs to aminopenicillins and cephalosporins. Thus, cephalosporins with a similar side-chain should be avoided in patients with IgE-mediated reactions to penicillin.[13,40] Moreover, in cases of IRs to penicillin, skin testing with alternative drugs (cephalosporins, carbapenems, aztreonam) is recommended prior to its administration. If negative, the drug should be given by increasing doses in an appropriate setting.[13]

In NIRs to aminopenicillins, both core structure and the whole molecule (core structure plus the amino-benzyl group of the side-chain) are recognized by T cells, although the latter plays a predominant role.[13] Despite the fact that cross-reactivity between penicillins, cephalosporins and carbapenems for T-cell reactions is very rare, it also demands investigation.[13,41]

4.1.2 – Sulfonamides: Sulfonamides are defined as drugs with a SO2-NH2 moiety. Sulfonamide antibiotics also contain an aromatic amine (N4 position) and a substituted ring (N1 position).[40] After βLs, sulfonamide antibiotics (namely sulfamethoxazole-SMX) are the most common cause of DARs.[40,42] SMX usually cause cutaneous NIRs and rarely IgE-mediated reactions[12,22,40] through the direct activation of T cells by covalent binding or acting as pro-hapten, respectively, as SMX is a chemically inert drug.[21,22,43,44] MPE is the most common presentation, but SJS/TEN were also described.[12,22,40,42]

About 40-80% of HIV patients treated with trimethoprim (TMP)-SMX develop a generalized MPE, usually accompanied by fever, while the incidence of skin rashes to TMP-SMX in healthy subjects is only 3% to 5%. The increased risk in HIV patients is probably related to immunologic and metabolic factors and to the frequent exposure to TMP-SMX.[42]

The N4 aromatic amine is critical for the development of NIRs to sulfonamide antibiotics and the N1 substituted ring appears to be important for IgE-mediated reactions. As non-antibiotic sulfonamides lack these structural components, cross-reactivity with sulfonamide antibiotics is not expected.[12,40,42] Conversely, all sulfonamide antibiotics should be considered to be cross-reactive.[11]

4.1.3 – Fluoroquinolones: This widely used class of broad-spectrum antibiotics can induce reactions mediated by IgE (hapten-carrier formation) and T cells (p-i mechanism).[6,45-47] that are estimated to occur in 2% to 3% of the treated patients.[45] IgE-mediated reactions are more common and usually severe, with anaphylaxis as the most frequent presentation. Urticaria/angioedema can also occur. NIRs are less frequent and include MPE, FDE, vasculitis, AGEP and SJS/TEN.[6,45-47] Moxifloxacin induces more severe reactions[6] and is the main culprit, followed by ciprofloxacin and levofloxacin.[6,46] As cross-reactivity between these antibiotics is common avoidance of all quinolones is advisable.[12,48]

4.2 – Nonsteroidal anti-inflammatory drugs: NSAIDs are responsible for 21% to 25% of reported ADRs, including immunological and non-immunological reactions. Depending on the clinical presentation and the presumable underlying mechanism, hypersensitivity to NSAIDs is classified in 2 groups and 5 subgroups (Table 2).[49] In the first group (≥ 75% of cases),[6] the putative mechanism is the inhibition of ciclooxigenase-1, hence hypersensitivity to multiple NSAIDs is observed regardless of their chemical structure and/or anti-inflammatory potency.[49]

The second group involves the selective reactions, probably with an underlying immunological mechanism: a) IgE-mediated is the proposed mechanism in cases of urticaria, angioedema and anaphylaxis induced by a single NSAID or a group of chemically related drugs.[49,50] Pyrazolones, paracetamol, ibuprofen, diclofenac and naproxen are the most common.[49] The last three compounds have a heteroaryl acetic group, presumably carrying a higher risk of anaphylaxis (OR 19.7);[51] b) NIRs, probably T-cell mediated, were also reported to be induced by a single NSAID or a group of chemically related drugs.[49-51] Cutaneous reactions, particularly MPE are the most frequent reaction. NSAIDs are the main cause of FDE and can also induce SJS/TEN (particularly oxicams).[49]

Diagnostic and management guidelines for children and adolescents with NSAIDs hypersensitivity, including a modified classification, were recently published considering specific clinical and epidemiological features.[52]

4.3 – Neuromuscular blocking agents (NMBAs): Immediate HRs during the perioperative period have been increasingly reported.[53] Most are mediated by IgE and less frequently related to direct stimulation of histamine release.[53-55]

IgE mechanism causes perioperative anaphylaxis (estimated incidence of 1:10 000 to 1:20 000) and any drug administered in this period can potentially induce it.[53] Different populations exhibit different patterns of sensitization.[7] NMBAs are the most common cause in Europe (50% - 70%), followed by antibiotics and latex. While latex is becoming a less common culprit, chlorhexidine is gaining importance and sugammadex is an emerging cause.[54]

Suxamethonium is the most frequent reported culprit, with a recent increment of rocuronium, vecuronium and pancuronium.[53,56,57] Sensitization to NMBAs seems to demand the presence of a substituted ammonium ion. In many cases, the reaction may occur at the first exposure, since a prior sensitization to another compound with a substituted ammonium ion (e.g. pholcodine) may have occurred.[5,54,55,57] Investigation of cross-reactivity between NMBAs is mandatory in diagnostic work-up.[58-62]

A new mast cell receptor MRGPRX2 (human Mas-related G-protein-coupled receptor member X2) was discovered and related with reactions to NMBAs not IgE-mediated,[54-55] which could explain the cases of perioperative anaphylaxis with negative skin testing (mast cell direct activation through this receptor).[54]

4.4 – Radiocontrast media: In the past the ionic high-osmolar RCM induced a high incidence of IRs due to the nonspecific release of vasoactive mediators.[6] Despite the introduction of nonionic (NI) low-osmolar RCM, hypersensitivity reactions (HSRs) are still a matter of concern. A recent European multicenter study suggests that at least 50% of the HRs to NI-RCM are caused by an immunological mechanism. Cross-reactivity was frequent among NI-RCM with a very similar chemical structure.[58] It is estimated that NI-RCM can cause IRs and NIRs in about 1% - 3% of applications.[59] IRs are mainly anaphylaxis, whereas NIRs predominantly manifest as mild skin eruptions occurring hours to days after RCM administration.[58-62]

4.5 – Biological modifiers: The biologic agents have been recently developed and are increasingly used. They comprise proteins such as cytokines and monoclonal antibodies (mAbs)[6,40] that differ from other drugs as they have high molecular-weight with a great immunogenic potential.[40] Three major groups of mAbs are in use: chimeric (-ximab), humanized (-zumab) and human antibodies (-mumab). They can induce reactions through different immunological mechanisms.[63,64] Clinical phenotypes include IRs (type I; infusion-related reactions, cytokine release, mixed reactions), type III and type IV delayed reactions.[64]

IgE-mediated reactions to basiliximab, infliximab and rituximab have been reported.[6,7,42] IgE antibodies to cetuximab specifically for alpha-1,3-galactose have been found in the majority of anaphylactic reactions.[7,65] Rare delayed anaphylaxis has been reported after exposures to omalizumab, trastuzumab, daclizumab, infliximab and basiliximab.[12]

Some patients present IgG antibodies to biologics that may block the effect of the drug or be involved in the development of HSRs.[64]

NIRS are rare but have been described, after rituximab (vasculitis, SSS)[7] and infliximab (SSS, SJS, DiHS).[40]

Desensitization allows a safe reintroduction of first-line biologic agent.[64,66]

4.6 – Antineoplastic agents: HSRs to antineoplastic agents are an increasing problem.[67,68] Any cytostatic can potentially expose the patient to the risk of an immune reaction. They can elicit either immediate (urticaria, bronchospasm, dyspnea, thoracic/abdominal pain, fever, anaphylaxis) or NIRs (macular/MPE, vasculitis). The severity of reactions ranges from mild symptoms to life-threatening anaphylaxis.[67]

HSRs are more common with platinum compounds (cisplatin, carboplatin, oxaliplatin), epipodophyllotoxins (teniposide, etoposide), asparaginase, taxanes (paclitaxel) and procarbazine. Doxorubicin and 6-mercaptopurine are rare culprits. HSR to carboplatin and oxaliplatin are particularly frequent (incidence: 12% - 17%), with more than 50% of the reactive patients developing moderate to severe

Table 2 - Classification of Hypersensitivity Reactions Induced by NSAIDs (adapted from [55])

Type of reaction	Clinical manifestations	Timing of reaction	Underlying disease	Cross-reactivity	Presumable mechanism	
NSAID-exacerbated respiratory disease (NERD)	Bronchospasm Nasal symptoms	Acute (usually immediate to several hours after exposure)	Asthma rhinosinusitis	Cross-reactive	Non-allergic	COX-1 inhibition
NSAID-exacerbated cutaneous disease (NECD)	Urticaria and/or angioedema		Chronic urticaria			
NSAID-induced urticaria/ angioedema (NIUA)						Unknown (probably COX-1 inhibition)
Single NSAID-induced urticaria/angioedema or anaphylaxis (SNIUAA)	Urticaria and/ or angioedema/ anaphylaxis		No underlying chronic disease	Non Cross-reactive	Allergic	IgE-mediated
Single NSAID-induced delayed reactions (SNIDR)	Various symptoms and organs involved (eg. MPE, FDE, SJS/TEN, nephritis)	Delayed onset (usually > 24h after exposure)				T cell-mediated

NSAID: Nonsteroidal anti-inflammatory drug; MPE: Maculopapular exanthema; FDE: Fixed drug eruption; SJS: Stevens-Johnson syndrome; TEN: Toxic epidermal necrolysis; COX- 1: Ciclooxigenase 1; IgE: Immunoglobulin E.

symptoms.[69]

Most reactions occur during the treatment (platinum derivatives and taxanes), although some appear hours after. Reactions to taxanes usually manifest during the first few minutes of the first or second infusion, whereas acute reactions to platinum agents usually occur after several cycles.[65,68,70-72]

Since these drugs are usually the first line therapy, patients can be desensitized[71] when no equally effective alternative drugs are available. The desensitization should follow the general considerations for these procedures published in a consensus paper for IRs[73] and NIRs.[74]

CONCLUSION

This exhaustive review, although the limitation of being non-systematic, pointed out that despite all advances, drug allergy is not yet fully established and understood. An exceptional contribution was brought by pharmacogenomics, even though a specific association has only been defined for a very limited number of drugs. Further investigation is needed to obtain clearer answers when managing each individual case of DA. The development of new biomarkers and a 'tailored-made' medicine is probably the future.

As knowledge in this field moves forward, new updates will be required.

CONFLICTS OF INTEREST

The authors declare they do not have any conflicts of interest and that they did not receive any financial support.

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IV. CHAPTER 2

Risk factors and other markers in drug allergy

Study II - “Allergy to beta-lactam antibiotics in children: Risk factors for a positive diagnostic work-up”

Allergol Immunopathol (Madr). 2020; 48 (5):417-423

Study III - “Psychological profiles of patients with suspected drug allergy”

Asia Pac Allergy. 2020 Oct;10 (4):e39

Study IV- “Obesity markers in patients with drug allergy and body fat as a predictor”

Ann Allergy Asthma Immunol 2021 Jul; 127 (1):100-108

Study V- “Dietary parameters in patients with drug allergy: assessing dietary inflammatory index ”

(submitted)

Allergol Immunopathol (Madr). 2020;48(5):417–423

Allergologia et immunopathologia

Sociedad Española de Inmunología Clínica, Alergología y Asma Pediátrica

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ORIGINAL ARTICLE

Allergy to beta-lactam antibiotics in children: Risk factors for a positive diagnostic work-up

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Received 15 October 2019; accepted 29 January 2020
Available online 24 May 2020

KEYWORDS
Drug allergy;
Beta-lactam antibiotics;
Children;
Allergy diagnostic work-up;
Risk factors

Abstract
Background: Allergy to beta-lactam (βL) antibiotics is highly reported in children, but rarely confirmed. Risk factors for a positive diagnostic work-up are scarce.

The primary aim was to characterize the cases of children with confirmed βL allergy, investigating potential risk factors. Secondary aims were to assess the prevalence of allergy to βL in this population and to confirm the safety of less extensive diagnostic protocols for milder reactions.

Methods: We reviewed the clinical data from all children evaluated in our Department for suspected βL allergy, over a six-year period.

Results: Two hundred and twenty children (53% females) with a mean age of 6.5 ± 4.2 years were evaluated. Cutaneous manifestations were the most frequently reported (96.9%), mainly maculopapular exanthema (MPE). The reactions were non-immediate in 59.5% of the cases.

Only 23 children (10.5%) were diagnosed with allergy to βL. The likelihood of βL allergy was significantly higher in children with a family history of drug allergy ($p < 0.001$) and in those with a smaller time period between the reaction and the study ($p = 0.046$). The probability of not confirming βL allergy is greater in children reporting less severe reactions ($p < 0.001$) and MPE ($p < 0.001$).

We found the less extensive diagnostic protocol in milder reactions safe, since only 4.2% of the children presented a positive provocation test (similar reaction as the index reaction).

Abbreviations: βL, beta-lactam; ENDA, European Network of Drug Allergy; sIgE, specific IgE; SPT, skin prick tests; IDT, intradermal tests; PPL, benzylpenicilloyl octa-l-lysine; MDM, sodium benzylpenilloate – minor determinant; PenG, penicillin G; AX/CL, amoxicillin/clavulanic acid; DPT, drug provocation test; MPE, maculopapular exanthema.

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https://doi.org/10.1016/j.aller.2020.01.005
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Conclusion: This study highlights family history of drug allergy as a risk factor for a positive diagnostic work-up. Larger series are required, particularly genetic studies to accurately determine future risk for βL allergy in children.
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Introduction

Beta-lactam (βL) antibiotics are the most commonly prescribed drugs in children[1,2] and also the most frequently implicated in drug allergy in these age groups.[3–6] Despite high suspicion rates and reports, only between 3.9% and 15.9% of the cases are confirmed by an allergy diagnostic work-up.[1,7–12]

These procedures are mandatory to define safe alternatives in the cases of confirmed allergy, but also to rule out the negative ones and prevent the negative impact of antibiotic allergy labels on clinical outcomes in children.[2,6,13]

There is no general consensus regarding the diagnostic protocols in paediatric ages and this topic is being highly debated. Moreover, studies on risk factors for a positive diagnostic work-up are scarce.

The primary aim of this study was to characterize the confirmed cases of βL allergy in children, investigating potential risk factors. Secondary aims were to assess the prevalence of allergy to this drug class in the studied population and to confirm the safety of less extensive diagnostic protocols for milder reactions.

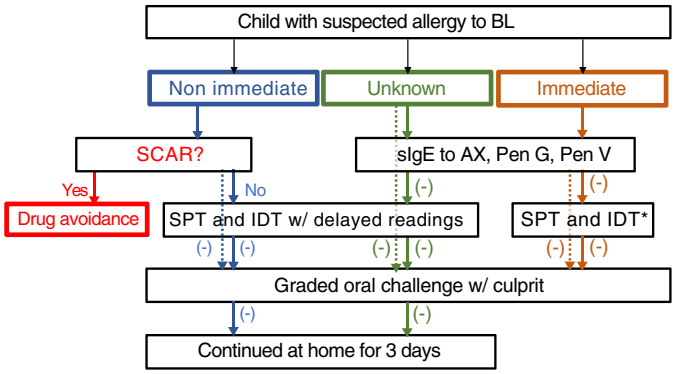

Figure 1 Algorithm for management suspected allergy to beta lactam antibiotics in children. In the case of positive sIgE skin test to the culprit drug, study is continued to confirm tolerance to a reasonable alternative (e.g. 3rd generation cephalosporins if allergic to aminopenicillins). Dotted lines: mild drug reaction. *Readings at 20 min only. HSR: hypersensitivity reaction; BL: betalactam antibiotics; sIgE: specific IgE, AX: amoxicillin; Pen: penicilloyl; IDT: intradermal tests; SPT: skin prick tests.

Material and methods

Patients

We retrospectively reviewed the clinical data from all children (younger than 18 years) assessed in our Allergy and Clinical Immunology Department for suspected βL allergy over a six-year period (January 2012 to December 2018).

Patients that did not complete the drug allergy diagnostic work-up were excluded.

Drug allergy work-up

For diagnostic purposes and in agreement with international guidelines, reactions were classified as immediate and non-immediate according to the time between drug intake and the onset of clinical symptoms.[14] In cases of multiple reactions (to single or multiple βL), the most severe reaction was considered.

The drug allergy work-up included a validated questionnaire[15] and, depending on the reaction type and severity, skin tests, specific IgE and/or drug provocation test (Fig. 1). All the diagnostic procedures followed the ENDA/EAACI (*European Network of Drug Allergy/European Academy of Allergy and Clinical Immunology*) recommendations[16–19] and were performed by trained specialists, in a day-care hospital under strict surveillance.

Serum-specific IgE antibodies (sIgE) (ImmunoCAP®, Thermo Fisher Scientific, Uppsala, Sweden) for penicillin G/V and amoxicillin were used, when evaluating immediate reactions or those with unknown time of occurrence. A cut-off value of ≥0.35 kU/L was considered positive.[19]

Skin prick tests (SPT) were performed and if negative, intradermal tests (IDT) with benzylpenicilloyl octa-l-lysine (PPL), sodium benzylpenilloate – minor determinant (MDM) (DAP® Penicillin, Diater, Madrid, Spain), penicillin G (PenG), amoxicillin/clavulanic acid (AX/CL) and ceftriaxone[16,17,19] were also performed. Other βL were tested according to the suspected drug. Late readings (after 48 h) were done in the cases of non-immediate reactions or those with unclear time of occurrence.

Given the low sensitivity of patch tests in the diagnosis of delayed reactions to βL,[17] they were not carried out routinely in all the cases of non-immediate reactions.

DPT with culprit drug were performed whenever skin tests and sIgE were negative and in the absence of other contraindications.[18,19] In children with mild reactions DPT was performed with the culprit drug without previous skin testing. In non-immediate reactions or when the time interval between exposure and reaction was not obvious by the clinical history, the patients were instructed to continue drug intake for two more days at home.[20]

The diagnosis of βL allergy was established when skin tests, specific IgE or DPT were positive. In such cases, an alternative βL was tested.

All legal guardians were fully informed about the procedures and signed an informed consent. The study was approved by the hospital ethics committee.

Statistical analysis

Data was summarized with mean and standard-deviation (SD) or absolute (*N*) and relative (%) frequencies. For analysis of the relationship of variables among patients with confirmed or excluded βL allergy the Chi-square test or Fisher exact test was used for categorical variables and when differences were significant the Bonferroni method was applied for pairwise comparisons. For continuous variables the Student *t*-test was used.

All statistical tests were carried out for two-tailed significance and a $p < 0.05$ was considered significant.

SPSS software (SPSS version 24.0, SPSS, Chicago, IL, USA) was used.

Results

Two hundred and twenty children (53.2% females) with a mean age of 6.5 years (SD = 4.2) were evaluated for suspected βL allergy and all completed the diagnostic work-up during the study period.

A further 29 children studied during this period were excluded since they did not complete the drug allergy diagnostic work-up. No analysis was performed referring to these patients' data.

The mean time that elapsed between the reaction and the clinical assessment was 2.9 years (SD = 3.3). The most frequently implicated drugs were AX/CL (47.7%) and amoxicillin (40.5%). βL were prescribed for tonsillitis in 32.7%, otitis in 22.7% and unspecified upper airways infection in 19.1%. Cutaneous manifestations were the most frequently reported presentation (96.9%) and the most common maculopapular exanthema (MPE). In 131 cases (59.5%) the reaction was non-immediate, in 10.5% immediate and in the remaining cases the time of onset was unknown. In 66 cases (30%) there was no history of previous exposure to the suspected drug, while 42 children (19%) had previous exposure with a similar reaction.

After completing the drug allergy work-up, 23 children (10.5%) were diagnosed with allergy to βL. Three of the positive cases belonged to the group that reported immediate reactions (3/23 cases, confirmation rate of 13%) and 16 to the group with non-immediate reactions (16/131, confirmation rate of 12.2%). It was possible to obtain a safe alternative βL in all of these positive cases. Table 1 summarizes the characteristics of all confirmed cases.

In order to investigate potential risk factors, we compared the two groups of children with confirmed and excluded βL allergy regarding demographic and clinical characteristics (Table 2). The likelihood of βL allergy was significantly higher in children with a family history of drug allergy (47.4% vs. 5.4%, $p < 0.001$) and in those with a shorter time interval between the reaction and the evaluation ($p = 0.046$). On the other hand, the probability of not confirming βL allergy is greater in children reporting less severe reactions ($p < 0.001$) and MPE ($p < 0.001$).

Regarding the safety of the less extensive diagnostic protocol in milder reactions, namely direct DPT with culprit drug without previous skin testing we found that it was safe since only seven (4.2%) of 167 children presented a positive DPT with a reaction similar to the index one.

Discussion

In this study, a large group of children with a suspected history of hypersensitivity reaction to βLs was assessed. Only 10.5% were confirmed to be allergic to βLs , after diagnostic work-up, similar to other studies.[1,8,10,11,20]

Although MPE represent the majority of suspected reactions caused by βL in children, our study confirmed a low positivity rate (3.9%; six confirmed in 155 suspected). However, in the absence of clearly distinctive characteristics of MPE related to viral infections, an allergy diagnosis work-up is mandatory in all cases.

Recently there has been intense debate regarding the diagnostic protocols in allergy to βL in children that has attracted renewed interest on this topic. Several studies have confirmed the low diagnostic value of skin tests in this age group with mild non-immediate reactions to βLs. In this setting, their utility is being questioned, especially considering that these are painful procedures that are poorly tolerated by children and, if negative, do not preclude the need for DPT to confirm the diagnosis.[4,7,8,20,21]

The knowledge of risk factors for a positive diagnosis could help support the decision to perform the full or the short work-up protocol and this was the primary aim of our study.

We found a significant association between a positive diagnostic work-up and family history of drug allergy ($p < 0.001$), shorter time interval between the suspected reaction and the study ($p = 0.046$) and more severe reactions ($p < 0.001$). The two last findings are consistent with another study.[7] Based on our results and the current literature, it is advisable to perform a drug allergy work-up as soon as possible, avoiding the first six weeks after the reaction.

To our knowledge, this is the first study showing a positive correlation between βL allergy in children and parental/sibling history of drug allergy. A recent study showed an increased risk for positive DPT to βL in children with parental history of drug allergy, but only in non-immediate reactions.[10] Family history of drug allergy was mainly but not exclusively related to βL (66.7%). The limited number of children with confirmed βL allergy did not allow a multivariate analysis and this is a limitation of this study. Also, no genetic studies were performed in our study. In immediate reactions, some polymorphisms in cytokine genes have been associated with βL allergy.[22] Another genome-wide association study in Spanish and Italian populations demonstrated the link between HLA-DRA genetic variants and penicillin allergy.[23]

Some studies reported that immediate reactions have a high probability of being confirmed after diagnostic work-up.[7,8] We did not find this correlation but the high percentage of reactions with unknown chronology (30%) in this study may have contributed to the final result.

The diagnosis of βL allergy in our study was based on positive skin tests (43.5%), namely in positive IDT (seven were

Table 1

Case	Gender	Age	Atopy	Family history of drug allergy	Type of reaction	Clinical manifestations	Culprit	Previous exposure	No. reactions	ΔReaction – study (months)	sIgE	ST results	Diagnostic DPT results
1	F	9	No	Yes	NI	EM	AX/CL	No	1	96	Nd	IDT + AX/CL (LR)	Nd
2	F	7	No	Yes	I	Anaphylaxis	AX	Yes	2	24	Neg	SPT, IDT -	+* (1 h)
3	M	12	No	Yes	U	U/AE	Pen	Yes	1	36	Neg	IDT + PPL	Nd
4	F	4	No	U.	NI (D3)	MPE	AX	Yes	1	12	Nd	Nd	+* (D5)
5	M	3	No	Yes	NI (D2)	MPE	AX	U.	1	12	Nd	Nd	+* (D6)
6	F	4	No	Yes	NI	Urticaria	AX	Yes	2	12	Nd	Nd	+* (D2)
7	M	5	No	Yes	NI	Urticaria	AX/CL	Yes	2	12	Nd	Nd	+* (8 h)
8	M	5	Yes	U.	NI (D8)	EM	AX/CL	U.	U.	U.	Nd	SPT, IDT (LR), patch -	+ (erythema + AE) (7 h)
9	M	7	Yes	Yes	U. (D1)	Urt/AE	AX	Yes	2	60	Neg	SPT, IDT (LR) -	+* (4 h)
10	M	3	Yes	Yes	U. (D6)	MPE	AX/CL	Yes	1	18	Nd	Nd	+* (5 h)
11	M	6	No	No	NI (D14)	SSLS	AX	U.	1	10	Nd	IDT + AX/CL (LR)	Nd
12	F	3	No	No	NI (D6)	SSLS	Cefuroxime	Yes	1	9	Nd	SPT, IDT (LR) -	+* (D7)
13	M	6	No	No	NI (D1)	FDE	AX	Yes	2	14	Nd	SPT, IDT (LR) patch -	+* (6 h)
14	M	14	No	No	I	Anaphylaxis	AX/CL	Yes	1	10	Neg	IDT + AX/CL and PPL	Nd
15	M	5	Yes	Yes	NI (D1)	SSLS	AX	Yes	1	8	Nd	SPT, IDT (LR) -	+* (D7)
16	M	12	No	U.	NI (D13)	DiHS	Ceftriaxone	Yes	1	8	Nd	IDT + ceftriaxone (LR)	Nd
17	M	16	No	No	NI (D7)	Vasculitis	AX/CL	U.	1	10	Nd	IDT + AX/CL (LR)	Nd
18	F	4	No	No	NI (D8)	SSLS	AX/CL	Yes	2	11	Nd	IDT + AX/CL (LR)	Nd
19	M	17	No	No	NI (D21)	MPE	Cefoxitin	Yes	1	12	Nd	IDT + Cefoxitin (LR)	Nd
20	M	2	No	Yes	I	Anaphylaxis	AX/CL	Yes	1	10	Neg	IDT + AX/CL	Nd
21	M	3	No	Yes	U.	MPE	AX/CL	Yes	2	12	Nd	Nd	+* (D2)
22	M	10	No	No	NI (D5)	SSLS	AX/CL	Yes	2	U.	Nd	IDT + AX/CL, PPL and MDM (LR)	Nd
23	F	4	No	No	NI	MPE	AX	Yes	2	13	Nd	Nd	+* (7 h)

Legend: U. – unknown; EM – erythema multiforme; NI – non-immediate; AX/CL – amoxicillin/clavulanic acid; IDT – intradermal test; nd – not done; ST – skin tests, Pen – penicillin; MPE – maculopapular exanthema; SSLS – serum sickness-like syndrome; Urt/AE – urticaria/angioedema; FDE – fixed drug eruption; DiHS – drug-induced hypersensitivity syndrome; LR: late reading. D: day, AE: angioedema; *: reproducible reaction.

Table 2 Demographic and clinical characteristics.

	Confirmed βL allergy ($n = 23$)	Excluded βL allergy ($n = 197$)	p value
Gender, n (%)			
Female	7 (30.4)	110 (55.8)	0.027
Male	16 (69.6)	87 (44.2)	
Age in years (R), Mean (SD)	4.4 (4.3)	3.5 (3.5)	0.262
ΔReaction − study, mean (SD)	1.9 (2.0)	3.0 (3.4)	0.046
Atopy, N (%)			
Yes	3 (13.6)	35 (19.6)	0.773
No	19 (86.4)	144 (80.4)	
Family history of drug allergy, n (%)			
Yes	9 (47.4)[a]	9 (5.4)[b]	<0.001
No	10 (52.6)[a]	158 (94.6)[b]	
Culprit drug, n (%)			
AX/CL	10 (43.5)	95 (48.2)	0.239
AX	9 (39.1)	80 (40.6)	
Penicillin	1 (4.3)	8 (4.1)	
Flucloxacillin	0 (0.0)	2 (1.0)	
2nd generation cephalosporin	2 (8.6)	6 (3.0)	
3rd generation cephalosporin	1 (4.3)	2 (1.0)	
Non-specified βL	0 (0.0)	4 (2.0)	
Type of reaction, n (%)			
Immediate	3 (13.0)	20 (10.2)	0.385
Non-immediate	16 (69.6)	115 (58.4)	
Unknown	4 (17.4)	62 (31.5)	
Clinical manifestations, n (%)			
Anaphylaxis	3 (13.0)[a]	0 (0.0)[b]	<0.001
Urticaria/Angioedema	4 (17.4)[a]	34 (17.4)[a]	
Bronchospasm	0 (0.0)[a]	2 (1.0)[a]	
Serum sickness-like syndrome	5 (21.7)[a]	0 (0.0)[b]	
Vasculitis	1 (4.3)[a]	0 (0.0)[b]	
Maculopapular exanthema	6 (26.1)[a]	149 (76.4)[b]	
DiHS/DRESS	1 (4.3)[a]	0 (0.0)[b]	
Fixed drug eruption	1 (4.3)[a]	0 (0.0)[b]	
Erythema multiforme	2 (8.7)[a]	0 (0.0)[b]	
Unspecified cutaneous symptoms	0 (0.0)[a]	8 (4.1)[a]	
Unspecified general symptoms	0 (0.0)[a]	2 (1.0)[a]	
Severity of reaction n (%)			
Mild	5 (21.7)[a]	142 (72.1)[b]	<0.001
Moderate	5 (21.7)[a]	52 (26.4)[a]	
Severe	13 (56.5)[a]	3 (1.5)[b]	

Different letters a, b denote significant differences among columns in each demographic or clinic characteristic according to Bonferroni's multiple comparison test.
Legend: Age in years (*R*) − age in years at the time of the reaction; SD − standard deviation; AX/CL − amoxicillin/clavulanic acid; DiHS/DRESS drug-induced hypersensitivity syndrome/drug rash with eosinophilia and systemic symptoms.

positive in late reading and three in immediate reading) or positive DPT (56.5%). The majority of the reactions were induced by DPT performed at day-care hospital (53.8%), with two reactions (28.6%) occurring during hospital stay and five (71.4%) when the children returned home. Six reactions to DPT (46.2%) occurred after continuing the tested drug at home. Except for one case (previously described as erythema multiform but presenting as erythema and angioedema after DPT), the clinical manifestations induced by re-exposure during DPT were similar to the index reaction. However, in non-immediate reactions, the time of onset did not reproduce the index reaction in the majority of cases. In two cases the reactions had a similar delay of index reaction, two occurred earlier and three later. There were no precise data in the remaining five cases.

In the study of these children, a less extensive protocol was followed in all mild reactions, including immediate and non-immediate ones, as usual in our Department. However, the majority of those mild reactions were non-immediate or with unknown chronology. Only six children reported mild

immediate reactions and they performed a direct DPT and none reacted. This protocol confirmed to be safe since only seven of the167 children presented a positive DPT similar to the index one. Globally DPT was positive in 6.2% of cases (13/210 children) and in 4.2% of children undergoing direct DPT without previous skin testing (7/167). The safety of this approach is in accordance with other studies concerning mild non-immediate reactions,[1,4,24] but few studies support the use of this strategy for mild immediate reactions to βLs in children.[10,25]

A crucial issue that lacks consensus is the optimal length for DPT in the diagnosis of non-immediate reactions, with protocols ranging from one to five days.[5,8,11,20,21,26] Some groups personalize the length of DPT according to the timing of the index reaction.[5,7] Although shorter protocols are more convenient and have fewer side effects, some authors defend that extended protocols may increase the sensitivity of DPT and the confidence in subsequent use of the drug.[4] A recent study showed that the two protocols are comparable concerning these issues.[5] This question was not evaluated by our study. We performed a three-day protocol (one in the hospital and two at home) and as described above, the majority of the reactions were induced by DPT performed at day-care hospital. The time of onset of reactions after continued DPT at home did not reproduce the index reaction in most of the cases, with some reactions after DPT occurring sooner and others later.

In conclusion, only 10.5% of the assessed children in this study were confirmed as allergic to βL. The less extensive diagnostic protocol showed to be safe in milder reactions. This study highlights first degree family history of drug allergy as a risk factor for a positive diagnostic work-up. Larger studies are required, particularly genetic studies to accurately determine future risk for βL allergy in children.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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Asia Pac Allergy. 2020 Oct;10(4):e39
https://doi.org/10.5415/apallergy.2020.10.e39
pISSN 2233-8276·eISSN 2233-8268

Asia Pacific allergy

Original Article

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Psychological profiles of patients with suspected drug allergy

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OPEN ACCESS

Received: Jun 24, 2020
Accepted: Oct 10, 2020

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Conflict of Interest
The authors have no financial conflicts of interest.

ABSTRACT

Background: Several studies demonstrate an important association between allergic diseases and patients' psychological characteristics.
Objective: To evaluate any differences in the psychological characteristics of patients studied for suspected drug allergy in comparison with healthy controls. A secondary aim was to assess differences between patients with confirmed versus excluded drug allergy, with respect to the clinical aspects.
Methods: The psychological characteristics of 115 consecutive patients >16 years-old, studied for suspected drug allergy were assessed. They were compared with healthy controls. Four validated questionnaires were used to evaluate anxiety, depression, alexithymia, and personality type.
Results: Eighty-eight patients completed the evaluation: 34 had confirmed drug allergy and 33 excluded. Forty-eight healthy subjects filled the 4 questionnaires. Increased neuroticism was associated with increased odds of belonging to the excluded drug allergy group (odds ratio [OR], 1.374; 95% confidence interval [CI], 1.173–1.609). Increased neuroticism (OR, 1.244; 95% CI, 1.065–1.453) and increased anxiety (OR, 1.210; 95% CI, 1.084–1.351) were associated with increased odds of confirmed drug allergy. However, higher extraversion decreased this likelihood (OR, 0.755; 95% CI, 0.643–0.888). The odds of having confirmed drug allergy was reduced by 79.7% (OR, 0.203; 95% CI, 0.060–0.694) for patients with 2 suspected drugs and by 84.6% (OR, 0.154; 95% CI, 0.029–0.809) for those with ≥3 in comparison to those with only one. Patients with moderate to severe reactions were more likely to have confirmed drug allergy (OR, 4.295; 95% CI, 1.105–16.693) than those with milder manifestations.
Conclusion: Our results highlight that patients with drug allergy have a distinctive psychological profile. Psychological assessment may help to identify patients that would benefit from a targeted intervention.

Keywords: Drug allergy; Psychological assessment; Anxiety; Depression; Alexithymia; Personality type

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Author Contributions

Conceptualization: Eunice Dias de Castro, Ana Leblanc, Josefina R. Cernadas. Data curation: Eunice Dias de Castro, Ana Leblanc. Formal analysis: Eunice Dias de Castro, Ana Leblanc, Joselina Barbosa, Laura Ribeiro. Methodology: Eunice Dias de Castro, Ana Leblanc, Joselina Barbosa, Laura Ribeiro, Josefina R. Cernadas. Project administration: Eunice Dias de Castro, Ana Leblanc, Josefina R. Cernadas. Writing - original draft: Eunice Dias de Castro. Writing - review & editing: Eunice Dias de Castro, Ana Leblanc, Joselina Barbosa, Laura Ribeiro, Josefina R. Cernadas.

INTRODUCTION

The relationship between psychological factors and allergic diseases has been observed by physicians for a long time and it is still a matter of debate. Those factors appear to influence the state of the disease [1]. In the last decades, several studies demonstrating an important association between allergic diseases and patients' psychological characteristics have been published. The majority involves skin and respiratory allergic diseases [2-12]. Patients with drug allergy appear to have more psychological disturbances than those with asthma or rhinitis [13], although studies of psychological assessment in the field of drug allergy are scarce. Moreover, these studies are quite heterogeneous, as they use very distinct methodologies and the classification of the type of reactions to drugs are often absent or unclear. In the majority of cases, it is not possible to understand whether the study involved drug hypersensitivity reactions, drug adverse reactions in general or true allergic reactions.

The primary aim of this study was to evaluate the psychological characteristics of patients studied for suspected drug allergy according to the results of the drug allergy diagnostic work-up (confirmed versus excluded drug allergy) investigating if there is any specific psychological profile.

It was also our objective to assess potential differences between the 2 groups regarding the clinical aspects of the reaction.

MATERIALS AND METHODS

Psychological characteristics of 115 consecutive patients older than 16 years-old, studied in our Allergy Department for suspected drug allergy, between March and September 2015, were assessed and compared with psychological characteristics of healthy controls. Four validated and self-completed questionnaires: Zung Anxiety scale [14-16], Zung Depression scale [16, 17], 20-item Toronto Alexithymia scale [18-21], and Eysenck questionnaire [22], were used.

The control group consisted of 55 healthy volunteers who were randomly recruited from patients' relatives and nonmedical faculty staff. They were asked to complete the 4 questionnaires.

Social-demographic data were also collected. Written informed consent was obtained by all individuals included in the study and the protocol was approved by the Hospital Ethics Committee (CE-72-2009).

Questionnaires

The Zung Self-Rating Anxiety Scale is a self- report assessment device built to measure anxiety levels. It includes 20 items and each question is scored on Likert-type scale of 1–4. The highest possible score is 80 and the results can be grouped according to the anxiety level as: normal anxiety (scores ≥ 20 and ≤44); moderate anxiety (scores ≥ 45 and <60); severe anxiety (scores ≥ 60 and <75) and extreme anxiety (scores ≥ 75) [14-16].

The Zung Self-Rating Depression Scale is 20-item self-report questionnaire that measures affective, psychological, and somatic symptoms linked to depression. There is a key with a

value (from 1 to 4) that correlates patients' responses to each statement. The highest possible score is 80 and the results can be grouped according to the depression level as: no depression (score < 29); mild depression (scores ≥ 29 and <37); moderate depression (scores ≥37 and ≤ 44) and severe depression (scores > 44) [16, 17].

The 20-item Toronto Alexithymia scale is a self-report measure of alexithymia. It consists of 3 subscales: difficulty in identifying feelings (7 items), difficulty in describing feelings (5 items), and externally oriented-thinking (8 items). Cutoff scores are as follow: ≤50 = no alexithymia; between 51 and 60 = borderline and ≥61 = alexithymia [18-21].

The Eysenck Personality Inventory (EPI) is a self-report personality test which can be used in several contexts. The version used was the original EPI with 57 items that was translated and validated for the Portuguese language. It measures 3 dimensions of personality: neuroticism (24 items), extraversion (24 items), and psychoticism (9 items). Each patient answer is rated according to an established key [22].

Drug allergy diagnostic work-up

The drug allergy diagnostic work-up was performed according to international guidelines [23], in order to confirm or exclude the suspected drug allergy. The type and severity of reaction, the type of suspected drug and the availability of validated skin tests and *in-vitro tests* were considered. It included a validated questionnaire (the drug hypersensitivity questionnaire developed by European Network of Drug Allergy- ENDA) [24] and, depending on the previous referred factors, skin tests (prick, intradermal and/or patch) [25, 26], specific IgE, and provocation test [27]. The diagnosis of drug allergy was confirmed when skin tests were positive for validated concentrations or when specific provocation test with the suspected drug when indicated was positive. On the other hand, drug allergy diagnosis was excluded if all diagnostic procedures, including specific provocation test with the suspected drug, were negative. Patients that did not complete the drug allergy diagnostic work-up or that did not reach a conclusive diagnosis were excluded.

Statistical analysis

The patient characteristics between the 3 groups according to drug allergy status (confirmed drug allergy vs. excluded drug allergy vs. control group) were reported using mean and standard deviation for continuous variables and absolute and relative frequencies for categorical variables. Significance of differences was also assessed using analysis of variance for continuous variables and chi-square test for categorical variables.

Multivariable multinomial regressions were then used to identify which demographic and psychological characteristics were related to drug allergy status, with the control group as the reference outcome. All predictor variables that reached the significance level of $p < 0.2$ at univariate analysis were considered for the final multivariable model. Continuous variables were checked for their linearity using the Box-Tidwell procedure [28]. The continuous variables extraversion and neuroticism do not support linearity in the logit. However, as the fit of the model with these as continuous predictors was much better than the fit with these as categorical predictors, extraversion, and neuroticism were retained as continuous. We also investigated potential interactions between covariates.

To create the most parsimonious model, variables that did not reach significance level of $p < 0.05$ in the multivariable model were backward eliminated one by one. Odds ratio (OR) and

95% confidence intervals (CIs) were calculated. In a sensitive analysis, we also calculated OR (95% CI) using resampling bootstrapping, based on 1,000 iterations and we identified the same possible predictor variables.

The 2 groups of patients studied for suspected drug allergy (confirmed drug allergy vs. excluded drug allergy) were compared for differences in clinical characteristics of the reaction with Student *t* tests or Mann-Whitney *U* test for continuous variables and chi-square tests for categorical variables.

A multivariable backward logistic regression analysis was performed to explore the baseline variables that independently predicted the occurrence of allergic symptoms. The predictors with a *p* value of <0.20 in univariate analyses were considered to be included in the logistic model. A multivariate logistic regression model was constructed using a *backward* elimination method. Results are reported as adjusted ORs and 95% CI. Interaction terms were also tested as candidate variables, but none of these terms entered the final model.

All statistical tests were carried out for 2-tailed significance and a $p < 0.05$ was considered significant.

The statistical significance threshold was set at $p < 0.05$. IBM SPSS Statistics ver. 24.0 (IBM Co., Armonk, NY, USA) was used.

RESULTS

Among 115 enrolled patients, 88 patients (77%) completed the drug allergy diagnostic work-up and the 4 psychological assessment questionnaires. From these 88 patients, 67 (76%) had a conclusive result: 34 had the final diagnosis of confirmed drug allergy and in 33 the drug allergy was excluded. Forty-eight healthy subjects filled the 4 psychological questionnaires.

Socio-demographic characteristics

Table 1 shows the socio-demographic characteristics of our sample. The sample size for the analysis included 34 patients with confirmed drug allergy, 33 patients with excluded drug allergy and a group of 48 controls. The 2 groups of patients and the control group were homogeneous concerning the majority of characteristics except for the item of academic studies ($p = 0.011$).

Psychological evaluation

According to the scores obtained in each psychological questionnaire, patients were classified in subgroups (**Table 2**). Due to the reduced number of individuals in some cases, comparison between subgroups was not possible.

Anxiety

Twenty-nine percent of patients with confirmed drug allergy and 27% of patients with excluded drug allergy, but only 2% of controls, presented moderate to severe anxiety (scores ≥ 60 and ≤74 in The Zung Self-Rating Anxiety Scale) [14-16]. No one presented extreme anxiety. More details are presented in **Table 2**.

Table 1. Socio-demographic characteristics

Characteristic	Controls (N=48)	Excluded drug allergy (N=33)	Confirmed drug allergy (N=34)	*p* value
Age (yr)	42.0 ± 10.0	43.0 ± 15.3	40.9 ± 12.9	0.796
Sex				0.340
Female	37 (77.1)	29 (87.9)	26 (76.5)	
Male	11 (22.9)	4 (12.1)	8 (23.5)	
Marital status				0.276
Single/divorced/widower	20 (41.7)	13 (39.4)	14 (41.2)	
Married	28 (58.3)	20 (60.6)	20 (58.8)	
Academics studies				0.011
≤6 yr	3 (6.3)	9 (27.3)	11 (32.4)	
7–12 yr	17 (35.4)	10 (30.3)	13 (38.2)	
>12 yr	28 (58.3)	14 (42.4)	10 (29.4)	
Employment status				0.098
Unemployed/retired/domestic	3 (6.3)	6 (18.2)	6 (17.6)	
Student/employed	45 (93.8)	27 (81.8)	28 (82.4)	
Hobbies				0.597
None	10 (20.8)	8 (24.2)	10 (29.4)	
One	13 (27.1)	9 (27.3)	5 (14.7)	
Multiples	25 (52.1)	16 (48.5)	19 (55.9)	
Descendants				0.239
1	30 (62.5)	19 (57.6)	21 (61.8)	
2	16 (33.3)	14 (42.4)	10 (29.4)	
≥3	2 (4.2)	0 (0)	3 (8.8)	

Values are presented as mean ± standard deviation or number (%).

Table 2. Psychological evaluation: results

Variable	Controls (N=48)	Excluded drug allergy (N=33)	Confirmed drug allergy (N=34)
Depression (scores)			
No depression (<29)	15 (31.3)	5 (15.2)	7 (20.5)
Mild depression (≥29 and <37)	22 (45.8)	15 (45.5)	8 (23.5)
Moderate depression (≥37 and ≤44)	4 (8.2)	5 (15.2)	10 (29.4)
Severe depression (>44)	7 (14.6)	8 (24.2)	9 (26.5)
Anxiety (scores)			
Normal anxiety (≥20 and <45)	47 (97.9)	24 (72.7)	22 (64.7)
Moderate anxiety (≥45 and <60)	1 (2.1)	7 (21.2)	8 (23.5)
Severe anxiety (≥60 and <75)	0 (0)	2 (6.1)	4 (5.9)
Alexithymia (scores)			
No Alexithymia (≤50)	37 (77.1)	19 (57.6)	18 (52.9)
Borderline (≥51 and <61)	7 (14.6)	2 (6.1)	6 (17.6)
Alexithymia (≥61)	4 (8.3)	12 (36.4)	10 (29.4)
Type of personality (scores)			
Neuroticism, >12	8 (16.7)	23 (69.7)	19 (55.9)
Extraversion, >12	23 (47.9)	17 (51.5)	11 (32.4)
Psychoticism, >5	18 (37.5)	12 (36.4)	8 (23.5)

Values are presented as number (%).

Depression

An important percentage of the analysed individuals scored above 44 in the The Zung Self-Rating Depression Scale [16, 17], signifying severe depression: 27% belonging to the confirmed drug allergy group, 24% to the excluded drug allergy group, and only 15% to the control group. The other subgroups are represented in **Table 2**.

Alexithymia

Twenty-nine percent of patients with confirmed drug allergy, 36% with excluded drug allergy, and only 8% of controls presented alexithymia (scores > 60 in 20-item Toronto Alexithymia scale) [18-21]. The remaining results are shown in **Table 2**.

Table 3. Psychological evaluation: comparison between studied groups

Variable	Controls (N=48)	Excluded drug allergy (N=33)	Confirmed drug allergy (N=34)	*p* value
Depression	33.1 ± 7.7	37.5 ± 9.3	39.4 ± 10.7	0.007
Anxiety	30.5 ± 6.5	39.1 ± 10.1	39.5 ± 11.2	<0.001
Alexithymia	42.3 ± 12.9	50.7 ± 17.1	49.6 ± 14.1	0.018
Type of personality				
Neuroticism	6.5 ± 4.5	13.4 ± 2.7	12.7 ± 3.4	<0.001
Extraversion	12.2 ± 3.4	12.2 ± 6.2	9.9 ± 6.1	0.095
Psychoticism	4.9 ± 1.7	4.6 ± 1.5	4.5 ± 1.4	0.609

Values are presented as mean ± standard deviation.

Type of personality

Respecting the 3 domains of the Eysenck Personality Inventory [22], the following cutoffs were applied: 12 to neuroticism, 12 to extraversion, and 5 to psychoticism. Fifty-six percent of patients from the group with confirmed drug allergy, 70% from the group with excluded drug allergy, but only 17% of controls scored above 12 for neuroticism. Thirty-two percent of patients with confirmed drug allergy, 52% with excluded drug allergy, and 48% of controls scored above 12 for extraversion, as shown in **Table 2**.

Analysis between groups

Table 3 shows the results of the psychological evaluation according to the mean scores obtained in the 4 questionnaires by study group, as well as comparison between them.

The following factors were found to be significantly (at 5% level) associated with excluded or confirmed drug allergy, compared with control group: academic status, depression, anxiety, alexithymia, and neuroticism. These factors were included in a multivariable model to identify independent factors associated with drug allergy status. Employment status and extraversion (as associated with the outcome at the 20% level) were also included in the multivariable model. The results of the multivariate model are displayed in **Table 3**.

Only neuroticism, extraversion, and anxiety remained significantly associated to drug allergy status.

Excluded drug allergy group vs. healthy group

Increased neuroticism was associated with an increased odds of belonging to the excluded drug allergy group (OR, 1.374; 95% CI, 1.173–1.609; excluded drug allergy vs. controls) (**Fig. 1**).

Confirmed drug allergy group vs. healthy group

Increased neuroticism (OR, 1.244; 95% CI, 1.065–1.453) and increased anxiety (OR, 1.210; 95% CI, 1.084–1.351) were associated with an increased odds of belonging to the confirmed drug allergy group. However, higher extraversion decreased this likelihood (OR, 0.755; 95% CI, 0.643–0.888) (**Fig. 1**).

Drug allergy

Tables 4 and **5** show the main groups of drugs and the main clinical manifestations, respectively. All the suspected drugs were presented in the **Table 4**, independently of being administered simultaneously or not. The study only included reactions presumably immunological mediated, including the ones involving nonsteroidal anti-inflammatory drugs (several times administered concomitantly with other drugs). Regarding the main clinical manifestations, the severest one was considered in the cases of multiple reactions. These reactions were recoded according to severity, to perform statistical analysis.

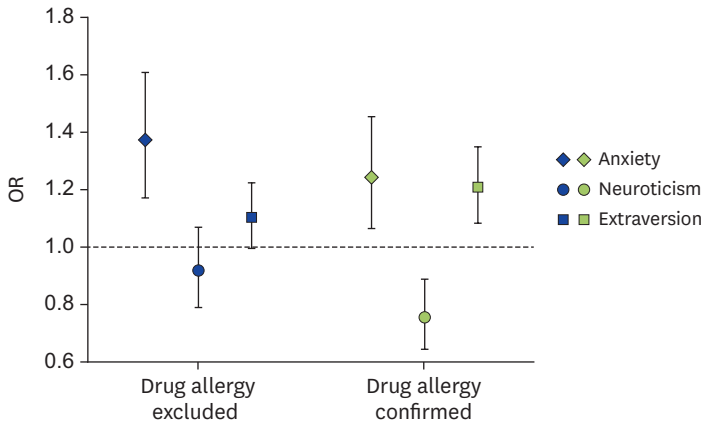

Fig. 1. Predictors of drug allergy status. OR: odds ratio for psychological features from multinomial logistic regression analysis predicting drug allergy (control group is the reference category) adjusted for neuroticism, extraversion, and anxiety. Error bars: 95% confidence interval.

Table 4. Groups of involved drugs

Group of drugs	Excluded drug allergy (N=33)	Confirmed drug allergy (N=34)
Suspected allergy		
Beta-lactam antibiotics		
Yes	22 (66.7)	17 (50.0)
No	11 (33.3)	17 (50.0)
Non beta-lactam antibiotics		
Yes	5 (15.2)	7 (20.6)
No	28 (84.4)	27 (79.4)
NSAID/analgesics		
Yes	15 (45.4)	22 (64.7)
No	18 (54.5)	12 (35.3)
Perioperative drugs	1 (3.0)	3 (8.8)
Yes	32 (97.0)	31 (91.2)
No		
Local anesthetics		
Yes	5 (15.2)	4 (11.8)
No	28 (84.4)	30 (88.2)
Other drugs		
Yes	6 (18.2)	7 (20.6)
No	27 (81.8)	27 (79.4)
Confirmed allergy		
Beta-lactam antibiotics		
Yes	0 (0)	14 (82.4)
No	22 (100)	3 (17.6)
Non beta-lactam antibiotics		
Yes	0 (0)	4 (57.1)
No	5 (100)	3 (42.9)
NSAID/analgesics		
Yes	0 (0)	8 (36.4)
No	15 (100)	14 (63.6)
Perioperative drugs		
Yes	0 (0)	3 (100)
No	1 (100)	0 (0)
Local anesthetics		
Yes	0 (0)	0 (0)
No	5 (100)	4 (100)
Other drugs		
Yes	0 (0)	5 (66.7)
No	6 (100)	2 (33.3)

Values are presented as number (%).
NSAID, nonsteroidal anti-inflammatory drugs.

https://doi.org/10.5415/apallergy.2020.10.e39

Table 5. Clinical manifestations

Clinical presentation	Excluded drug allergy (N=33)	Confirmed drug allergy (N=34)
Anaphylaxis	1 (3.0)	12 (34.3)
Cardiovascular symptoms	0 (0)	2 (5.7)
Respiratory symptoms	0 (0)	3 (8.8)
Urticaria/angioedema	19 (57.6)	10 (28.6)
Thrombocytopenia	0 (0)	1 (2.9)
MPE/erythema/pruritus	8 (24.2)	5 (14.3)
Stevens-Johnson Syndrome	0 (0)	1 (2.9)
Unspecified symptoms	2 (6.1)	0 (0)
Unknown	3 (9.1)	0 (0)

Values are presented as number (%).
MPE, maculopapular exanthema.

Clinical characteristics of the reaction

The clinical characteristics of the reactions according to the drug allergy diagnostic work-up, are presented in the **Table 6**. The majority of patients (70.6%) with confirmed drug allergy referred only one suspected drug while most of patients (61.0%) with excluded drug allergy had at least 2 suspected drugs (excluding drugs simultaneously administrated) ($p = 0.016$).

In terms of type of reaction (immediate vs. nonimmediate onset), a significant higher percentage of patients with excluded drug allergy could not describe the type of reaction and it was classified as unknown (36.0% vs. 11.7%, $p = 0.049$). Finally, regarding the severity of reaction, the group of patients with confirmed drug allergy presented more severe reactions compared with the group with excluded drug allergy (47.0% vs. 3.0%, $p < 0.001$) (**Table 6**).

Factors associated with drug allergy diagnosis

The odds of having drug allergy confirmed was reduced by 79.7% (OR, 0.203; 95% CI, 0.060–0.694) for those patients with 2 suspected drugs and by 84.6% (OR, 0.154; 95% CI, 0.029–0.809) for those patients with 3 or more suspected drugs compared to those with only one suspected drug. Also, patients with moderate to severe manifestations were more likely to have drug allergy confirmed (OR, 4.295; 95% CI, 1.105–16.693) than those with mild manifestations (**Table 7**).

Table 6. Characteristics of drug allergic reaction

Characteristic	Excluded drug allergy (N=33)	Confirmed drug allergy (N=34)	*p* value
No. of suspected drugs*			0.016
1	13 (39.0)	24 (70.6)	
≥2	20 (61.0)	10 (29.4)	
No. of reactions	2.0 (1.0–3.0)	2.0 (1.0–3.0)	0.903
Type of reaction			0.049
Unknown	12 (36.0)	4 (11.7)	
Immediate	12 (36.0)	16 (47.1)	
Nonimmediate	9 (27.0)	14 (41.2)	
Severity of reaction			<0.001
Mild	13 (39.4)	5 (1.0)	
Moderate	19 (57.6)	13 (38.0)	
Severe	1 (3.0)	16 (47.0)	

Values are presented as number (%) or median (interquartile range).
*Except for simultaneous administration of drugs.

https://doi.org/10.5415/apallergy.2020.10.e39

Table 7. Factors associated with drug allergy diagnosis

Predictor	OR	95% CI	*p* value
No. of suspected drugs*			
1	Reference		
2	0.203	0.060–0.694	0.011
≥3	0.154	0.029–0.809	0.027
Severity of reaction			
Mild	Reference		
Moderate/severe	4.294	1.105–16.693	0.035

OR, odds ratio; CI, confidence interval.
Only variables retained in the final model.
*Except for simultaneous administration of drugs.

DISCUSSION

The management of patients with drug allergy can be a challenge, not only due to a complex and time-consuming diagnostic work-up, but also because of the impact that this unpredictable and potentially severe condition may have in the patient. There are some studies suggesting that these patients have some psychological features that should be considered as they can influence this process [29-31]. However, very few involve patients with true drug allergy. Many are based only on medical records of drug allergy [32-35], mainly reported by patients, or in a diagnosis based only on clinical history [36].

Our study includes only patients with a reliable history of drug allergy that underwent an allergy diagnostic work-up with a conclusive result. The 2 groups of patients (excluded drug allergy and confirmed drug allergy) showed increased neuroticism assessed by the EPI test [22].

Beside increased neuroticism, the group of patients with confirmed drug allergy also presented increased anxiety and decreased extraversion.

These results are quite different from other studies that assessed psychological characteristics of patients studied for suspected drug allergy and the divergences may probably be explained by different methodologies used. The type of personality was rarely analysed [37] and the majority of drug provocation tests (DPTs) were performed with an alternative drug, not permitting a conclusive result [37-39]. One study that evaluated the type of personality, besides depression, revealed that globally those patients presented higher depression and hysteria, but mainly those with a history of less severe reactions and unlikely reactions [37]. Some authors found higher levels of somatization [38], anxiety [29, 30], panic and/or depression [30] in patients admitted for DPTs. Finally, patients with multiple drug intolerance syndrome (MDIS) revealed higher levels of anxiety, depression, somatization, and alexithymia [39], a minor capability of expressing emotions, but a higher expression of depression feelings [40]. We also found high levels of anxiety, depression, and alexithymia, in the 2 groups of patients with confirmed drug allergy and excluded drug allergy. However, these associations lost their significance, in a multivariate model.

In our study, the group of patients with confirmed drug allergy revealed more psychological disturbances (higher anxiety and neuroticism, lower extraversion) than the group with excluded drug allergy (higher neuroticism) when compared to controls. To our knowledge, only one previous study performed a similar assessment, according to the final drug allergy diagnosis [41]. However, these authors evaluated exclusively anxiety and the presence of

panic attack symptoms. They concluded that patients with a history of drug hypersensitivity have higher levels of anxiety, though not related with the results of diagnostic work-up. They found higher rates of panic symptoms in patients with proven reactions. However, this association was lost in the multiple logistic regression analysis.

Regarding the clinical characteristics of the reaction, we found that the group of patients with excluded drug allergy referred a higher number of suspected drugs. This result is in accordance with studies involving patients with MDIS, whose allergy tests were all negative [39, 40].

In our study, the group of patients with a confirmed diagnosis presented more severe reactions and a lower number of suspected drugs. These aspects were predictive of a positive study. These patients also showed high anxiety, high neuroticism, and lower extraversion, as previously described. However, due to the reduced number of individuals in some subgroups, it was not possible to determine if patients with more severe reactions had high anxiety as in other studies [31, 42].

The sample size is one of the limitations of our study that did not allow for subgroup analysis (by type of reaction, drug class, psychological features). Another is that the clinical psychological assessment was based on questionnaires, that are screening instruments and do not replace a more accurate method such as psychological interview.

Also, the time elapsed between the reaction and drug allergy work-up diagnosis was not considered. Consecutive patients were included independently of the time interval of the reaction although it is known that for some drugs sensitivity of the work-up diagnosis decreases over time [43].

On the other hand, the prospective study design, including all potential subjects, without selection bias, a complete allergy diagnostic work-up and an embracing psychological evaluation are the main strengths of our study.

The results achieved are very relevant, including those respecting the clinical aspects of the reaction and the final diagnosis probability. The finding that milder reactions have less probability of being related to drugs, if supported by larger studies, can lead somehow to changes in the future in some extensive and time-consuming protocols.

In conclusion, our results highlight, for the first time, that patients with confirmed drug allergy present a distinct psychological profile. The importance of these results in clinical practice is that the psychological assessment of patients with drug allergy can represent an important and advisable tool as it allows to identify patients that would benefit from psychological intervention.

ACKNOWLEDGEMENTS

The authors would like to thank to Dr. Virgínia Rebelo for her collaboration in the selection of psychological assessment questionnaires.

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Ann Allergy Asthma Immunol 127 (2021) 100–108

Contents lists available at ScienceDirect

Obesity markers in patients with drug allergy and body fat as a predictor

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ARTICLE INFO

Article history:
Received for publication November 24, 2020.
Received in revised form March 13, 2021.
Accepted for publication March 18, 2021.

ABSTRACT

Background: Obesity is a chronic low-grade inflammation state associated with several diseases.
Objective: To investigate a potential link between drug allergy and obesity, exploring whether the association depends on the type (immediate vs nonimmediate) or the severity of the reaction.
Methods: Anthropometric measurements, bioimpedance, and biochemical analysis, including serum adipokines, were performed in 90 consecutive adult patients studied for suspected drug allergy. Logistic regression models were developed to identify predictors of drug allergy.
Results: A total of 84 patients completed the diagnostic workup (78.6% women; mean age 39.58 ± 13.3 years). Drug allergy was confirmed in 39 patients and excluded in 45 (controls). Regarding body mass index, 42.2% had normal weight and 55.3% were overweight/obese. A total of 58% of women and 41% of men fulfilled the criteria for central obesity. Patients with drug allergy exhibited considerably higher body mass index, waist and hip circumferences, waist-hip ratio, fat mass, body fat percentage (BFP), trunk fat mass, leptin levels, and leptin-adiponectin ratio than controls. Similar results were obtained in the subgroup with immediate reactions, compared with the nonimmediate or **u**nknown reactions. The higher the BFP and the number of reactions, the greater the odds of drug allergy (odds ratio [OR], 1.07; 95% confidence interval [CI], 1.01-1.14 and OR, 2.82; 95% CI, 1.31-6.10, respectively). An immediate reaction was also a predictor of drug allergy (OR, 3.81; 95% CI, 1.30-11.14, $P = .02$), compared with nonimmediate or unknown reactions. In patients with drug allergy, BFP was a predictor of having an immediate reaction (OR, 1.12; 95% CI, 1.02-1.24, $P = .02$).
Conclusion: Our study illustrates, for the first time, evidence of a link between obesity and drug allergy, particularly immediate reactions. The BFP emerged as a potential predictor of drug allergy.
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Introduction

Drug allergy concerns adverse reactions to drugs that are mediated by immunologic mechanisms.[1] It is a complex and challenging field given that these reactions have a great heterogeneity of clinical presentations that can be supported by different underlying mechanisms, and they are usually unpredictable and potentially severe.[1-3] A multiplicity of factors such as the chemical structure of the molecule, the nature of exposure to the drug, and factors related to the patient, may control this process, influencing the risk of sensitization and the severity of clinical symptoms. Although most of the risk factors have not yet been established, a disturbed immunologic status is likely to have an important role, decreasing the threshold required to stimulate a response.[1,4,5]

In the past decades, allergic diseases increased in parallel with obesity[6,7] and several studies correlated these 2 diseases. Most studies involve patients with asthma[8-15] but the same association has been also described in allergic rhinitis[16-20] and atopy.[7,21,22] There are no published studies involving patients with drug allergies.

Some hypotheses have been advanced to explain the potential link between obesity and allergic diseases[6,8,20,23,24] but further investigation is needed.

Adipose tissue (AT) emerged as a major metabolic active organ, producing a variety of bioactive peptides termed adipokines regulating physiological and pathologic processes, including immunity and

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Disclosures: The authors have no conflicts of interest to report.
Funding: The authors have no funding sources to report.

https://doi.org/10.1016/j.anai.2021.03.014
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inflammation.[25-27] It is now widely accepted that the cross-talk between immune cells and adipocytes can be mediated by adipokines.[24] There is evidence that some adipokines, namely leptin and adiponectin, may also be involved in allergic inflammation through modification of immunologic responses.[24,28,29] Leptin has proinflammatory activities, whereas adiponectin is an anti-inflammatory adipokine.[8,9] Moreover, obesity is considered a chronic low-grade inflammation state[10,12,20,23,27,30,31] and it is associated with an up-regulation of proinflammatory and a down-regulation of anti-inflammatory adipokines,[8,12,23,25] particularly central obesity.[31,32]

The aim of this study was to investigate a potential link between drug allergy and obesity. Another objective was to explore if the association depends on the type of the allergic reaction (immediate vs nonimmediate) and/or the severity of the reaction.

Therefore, we intended to test the following hypotheses: (1) patients with a drug allergy have higher obesity markers comparing with controls, and (2) patients with drug allergy present a worse inflammatory profile (higher levels of proinflammatory adipokines and lower levels of anti-inflammatory adipokines) comparing with controls.

Methods

Study Population

We prospectively evaluated 90 adult patients, studied in our allergy department for suspected drug allergy from September 2017 to October 2018. A complete and detailed history was performed through a validated questionnaire (the drug hypersensitivity questionnaire developed by the European Network of Drug Allergy), during the first evaluation in our outpatient clinic.[33] Patients with a suggestive history of drug allergy were referred to a day hospital for diagnostic workup as per usual in our clinical practice. Patients were contacted by phone the day before their first visit to the day hospital and were invited to participate. If they agreed, overnight fasting was recommended. Only patients with reactions in the previous 5 years were included. The patient inclusion process is outlined in Figure 1. Sociodemographic data and information regarding sleep, number of meals, and exercise habits were collected. Written informed consent was obtained from all participants included in the study and the protocol was approved by the hospital ethics committee (CE-66-2016).

Drug Allergy Diagnostic Workup

The drug allergy diagnostic workup was performed in the day hospital, guided by the clinical history and in accordance with international guidelines.[1] The type and severity of the reaction, the suspected drug, and the availability of validated skin tests and in-vitro tests were considered and included skin tests (prick and intradermal),[34,35] specific immunoglobulin E (IgE), and drug provocation test.[36]

The diagnosis of drug allergy was confirmed when skin tests were positive for validated concentrations or when a specific provocation test with the suspected drug was positive. Drug allergy was excluded if all diagnostic procedures including drug provocation tests with the suspected drug were negative. Patients that did not complete the diagnostic workup or those who did not obtain a conclusive diagnosis were excluded.

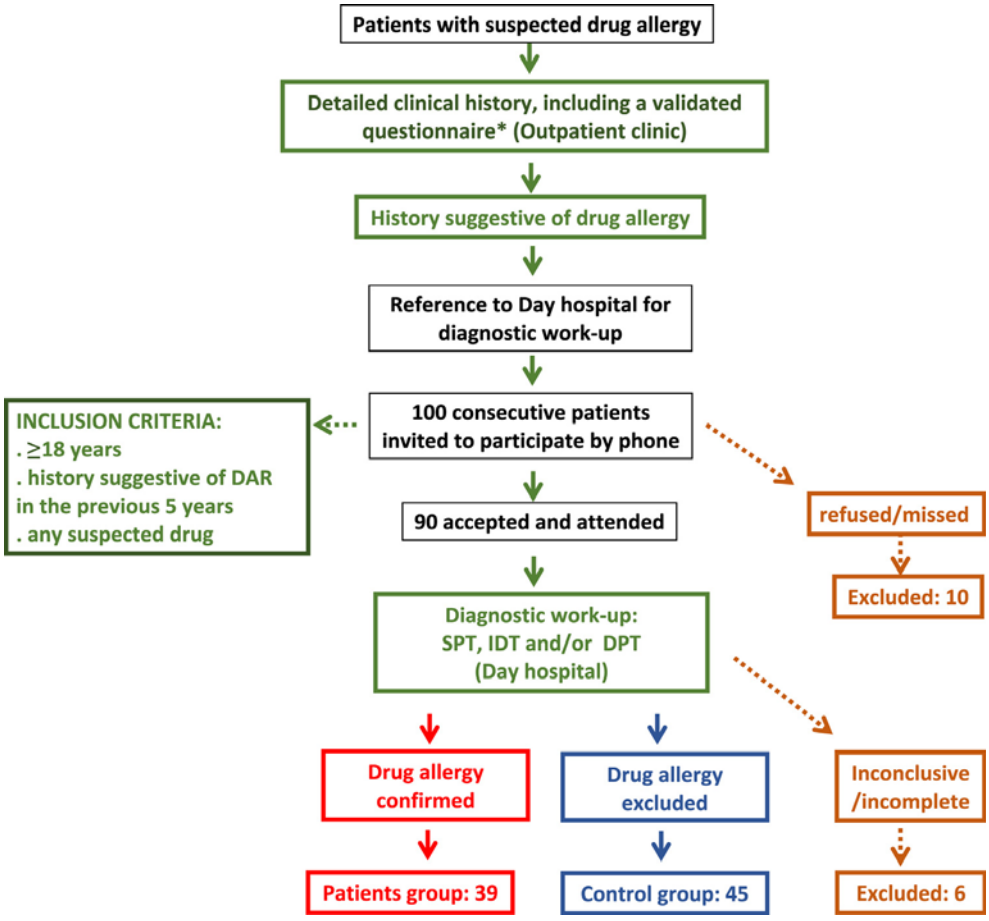

Figure 1. Algorithm for patients' inclusion. The asterisk represents the drug hypersensitivity questionnaire developed by European Network of Drug Allergy- ENDA).[33] DAR, drug allergic reaction; DPT, drug provocation test; IDT, intradermal tests; SPT, skin prick tests.

Anthropometric Measurements and Body Composition

Each participant underwent height (to the nearest 0.5 cm) and body weight (to the nearest 0.1 kg) measurements while wearing light clothing and no shoes. Body mass index (BMI) was calculated by dividing weight by squared height and expressed in kg/m^2. Individuals were classified as normal weight (≥18 and <25 kg/m^2), overweight (≥25.0 and <30 kg/m^2), and obese (≥30.0 kg/m^2) according to the BMI categories defined by World Health Organization guidelines.[37]

Waist circumference (WC) was measured with a flexible tape at the level midway between the lowest rib and the iliac crest. Central obesity was defined, based on the International Diabetes Federation criteria (IDF), as WC of greater than or equal to 0.80 m in women and greater than or equal to 0.94 m in men.[38,39] Hip circumference (HC) was measured at the level of the widest circumference over the great trochanters. Both circumferences were measured with patients standing at the end of gentle expiration. The waist-hip ratio was also calculated.[37]

Body composition, including fat mass (in kilograms and percentage), was assessed by bioimpedance (Inbody 230 Body Composition Analyzer [InBody Co, Ltd, Seoul, South Korea; tetra polar 8-point tactile electrodes [BioSpace, Inc, Urbandale, Iowa]).

Biochemical Analysis

Blood samples for leptin and adiponectin determination were obtained between 8 am and 9 am after an overnight fast. After clotting at 4°C, the serum was separated by centrifugation and stored at −70°C until assay. Serum leptin and serum adiponectin concentration were measured with the double antibody sandwich enzyme-linked immunosorbent assay (ELISA) assay by using an antibody specific for human leptin and for human adiponectin, respectively (Mercodia Leptin ELISA and Mercodia Adiponectin ELISA, Mercodia AB, Uppsala, Sweden).

Blood samples for glucose, total cholesterol, high-density lipoprotein cholesterol (HDL-cholesterol), and triglycerides in serum were obtained in the same conditions with anticoagulant-treated tubes and their concentrations were determined using standard techniques. The low-density lipoprotein cholesterol (LDL-cholesterol) levels were calculated according to the manufacturer's instructions (Roche, Rotkreuz, Switzerland).

Other Assessments

The IDF criteria were used to determine the presence of the metabolic syndrome.[39]

Statistical Analysis

Data were entered and analyzed using the Statistical Package for Social Sciences version 25 (IBM Corporation, Armonk, New York) and statistical significance was defined as $P < .05$.

For continuous quantitative variables, the existence of normal distribution was tested through histogram observation, kurtosis, and skewness analysis and using the Kolmogorov-Smirnov test. To describe variables, we used central tendency measures (mean and median) and dispersion measures (SD and percentiles 25-75) for quantitative variables and absolute numbers and percentages for qualitative variables. To analyze differences between groups in categorical variables, the χ^2 test and the Fisher's exact test were used. To compare continuous variables with normal and non-normal distribution between groups, an independent samples *t* test and Mann-Whitney test was used, respectively. Correlations were evaluated using the Pearson and the Spearman correlation tests for continuous symmetrical and asymmetrical variables, respectively.

No adjustment for multiple comparisons was performed. Logistic regression models were developed to evaluate predictors of drug allergy and predictors of an immediate allergic reaction, adjusting for potential confounders using a stepwise regression with a forward inclusion approach.

Results

Study Population and Drug Allergy Workup

A total of 84 patients completed the diagnostic workup: 66 (78.6%) were women and the mean age was 39.58 (±13.3) years (range 18-77).

Beta-lactam antibiotics (ßL antibiotics) were the most common suspected drugs (66 of 84 patients, 78.6%), followed by non-ßL antibiotics (12 of 84, 14.3%), general anesthetics (12 of 84, 14.3%) and nonsteroidal anti-inflammatory drugs (9 of 84 patients; 10.7%). The main clinical presentations were maculopapular exanthema (34.6%), urticaria/angioedema (24.4%), and anaphylaxis (25.6%). Regarding the type of reaction, 53.6% of the patients described immediate and 38.1% nonimmediate reactions. After completing the drug allergy workup, 39 patients (46%) had the final diagnosis of confirmed drug allergy.

The culprit drug was a ßL antibiotic in 27 cases, a general anesthetic in 3 cases, a nonsteroidal anti-inflammatory drug in 2, a proton pump inhibitor in 2, a radiocontrast media in 2, a corticosteroid, and H_2 antihistamine in 1 case. One patient had a positive diagnostic workup with 2 distinct drugs (1 ßL antibiotic and 1 non-ßL antibiotic).

The likelihood of confirmed drug allergy vs a negative diagnostic workup was significantly higher in the cases involving immediate reactions, severe reactions, anaphylaxis, a higher number of reactions, and a shorter interval of time between reaction and study.

Table 1 summarizes the sociodemographic and the clinical characteristics of patients with confirmed drug allergy and controls (those with excluded drug allergy) and a comparison between the 2 groups. Few data are missing and they are mainly sociodemographic characteristics.

Anthropometric Measurements and Body Composition

Regarding BMI, 42.2% of patients had normal weight, 36% were overweight and 19.3% were obese. Two individuals were underweight. Men had a mean WC of 92.68 (±11.7) cm and women had a mean WC of 82.91 (±12.5) cm. According to the IDF criteria, 57.6% of the women and 41.2% of the men presented central obesity.

In Table 2, we can see the associations between those parameters and the allergy diagnostic workup results. Patients with drug allergy exhibited significantly higher obesity-related parameters, either anthropometrics, either assessed by bioimpedance, than controls: BMI ($P = .02$), WC ($P = .03$), HC ($P = .03$), waist-hip ratio, ($P < .001$) fat mass ($P = .001$), body fat percentage ([BFP]; $P = .002$), and trunk fat mass ($P = .001$).

There were no significant differences between the 2 groups regarding lean mass, fat-free mass, or total body water.

Adipokine Levels and Other Biochemical Parameters

Except for leptin levels and leptin-adiponectin ratio, no other significant differences were observed between patients with confirmed drug allergy and patients with excluded drug allergy with respect to the evaluated biochemical parameters (Table 2). Patients with confirmed drug allergy presented significantly higher leptin levels and leptin-adiponectin ratio.

Other Assessments

We found no differences between the drug allergy group and the control group regarding other evaluated parameters (Table 2). A total of 15 patients met the criteria for metabolic syndrome,[39] 9 in the

Table 1
Sociodemographic and Clinical Characteristics of Patients

Characteristic	N	Confirmed drug allergy (N = 39)	N	Excluded drug allergy (N = 45)	*P* value
Sex, n (%)	39		45		.85
Female		31 (36.9)		35 (41.7)	
Male		8 (9.5)		10 (11.9)	
Age in y, Mean (SD)	39	41.0 (13.9)	45	38.4 (12.7)	.37
Academics studies, n (%)	33		40		.25
≤6 y		4 (5.5)		10 (13.7)	
7-12		15 (20.6)		19 (26.0)	
>12		14 (19.2)		11(15.1)	
Atopy, n (%)	39		45		.17
Yes		15 (17.9)		11 (13.1)	
No		24 (28.6)		34 (40.5)	
Comorbidities, n (%)	39		44		.38
Yes		25 (30.1)		24 (28.9)	
No		14 (16.9)		20 (24.1)	
Diabetes, n (%)	39		44		.72
Yes		1 (1.2)		1 (1.2)	
No		38 (45.8)		43 (51.8)	
Dyslipidemia, n (%)	39		44		.28
Yes		4 (4.8)		2 (2.4)	
No		35 (42.2)		42 (50.6)	
Hypertension, n (%)	39		44		.10
Yes		6 (7.2)		2 (2.4)	
No		33 (39.8)		42 (50.6)	
Asthma, n (%)	39		44		.29
Yes		6 (7.2)		4 (4.8)	
No		33 (39.8)		40 (48.2)	
Allergic rhinitis, n (%)	39		44		.41
Yes		10 (12.0)		8 (9.6)	
No		29 (34.9)		36 (43.4)	
Food allergy, n (%)	39		44		.53
Yes		0 (0.0)		1(1.2)	
No		39 (47.0)		43 (51.8)	
Anaphylaxis[a], n (%)	39		44		.28
Yes		0 (0.0)		2 (2.4)	
No		39 (47.0)		42 (50.6)	
Daily medication, n (%)	39		44		.14
Yes		24 (28.9)		20 (24.1)	
No		15 (18.1)		24 (28.9)	
Oral antidiabetics or insulin, n (%)	39		44		.72
Yes		1 (1.2)		1 (1.2)	
No		38 (45.8)		43 (51.8)	
Statins or fibrates, n (%)	39		44		.28
Yes		4 (4.8)		2 (2.4)	
No		35 (42.2)		42 (50.6)	
ACEI or ARAII, n (%)	39		44		.17
Yes		5 (6.0)		2 (2.4)	
No		34 (41.0)		42 (50.6)	
Diuretics, n (%)	39		44		.53
Yes		0 (0.0)		1 (1.2)	
No		39 (47.0)		43 (51.8)	
Family history of drug allergy, n (%)	38		44		.25
Yes		3 (3.7)		1 (1.2)	
No		35 (42.7)		43 (52.4)	
Δ reaction-study in y, median (SD)					
≤1 y		11 (29.7)		8 (17.8)	**.04**
>1 and ≤2 y	37	6 (16.2)	45	15 (33.3)	
>2 and ≤4 y		7 (18.9)		15 (33.3)	
>4 and ≤5 y		13 (35.1)		7 (15.6)	
Type of reaction, n (%)	39		45		**.002**
Immediate		28 (33.3)		17 (20.2)	
Nonimmediate/unknown		11 (13.1)		28 (33.3)	
Clinical manifestations, n (%)	38		40		NA[b]
Anaphylaxis		18 (23.1)		2 (2.6)	
Urticaria and angioedema		9 (11.5)		10 (12.8)	
Maculopapular exanthema		7 (9.0)		20 (25.6)	
Cardiovascular symptoms		0 (0.0)		2 (2.6)	
Bronchospasm		2 (2.6)		2 (2.6)	
Fixed drug eruption		1 (1.3)		1 (1.3)	
Unspecified general symptoms		1 (1.3)		3 (3.9)	
Anaphylaxis, n (%)					
Yes	38	18 (23.1)	40	2 (2.6)	**<.001**
No		20 (25.9)		38 (48.7)	
Maculopapular exanthema, n (%)					
Yes	38	7 (7.9)	40	20 (25.9)	**.003**
No		31 (39.7)		20 (25.9)	

(*continued*)

Table 1 (*Continued*)

Characteristic	N	Confirmed drug allergy (N = 39)	N	Excluded drug allergy (N = 45)	*P* value
Severity of reaction n (%)	37		40		**<.001**
Mild		6 (7.8)		25 (32.5)	
Moderate		11 (14.3)		14 (18.2)	
Severe		20 (26.0)		1 (1.3)	
Number of reactions, Median (IQR)[c]	39	1 (1-2)	45	1 (1-1)	**.003**
Number of suspected drugs, Median (IQR)[c]	39	1 (1-2)	45	1 (1-1)	.13
Suspected drug, n (%)					
ßLantibiotics	39	32 (38.1)[d]	45	34 (40.5)	.47
Non- ßLantibiotics		4 (4.8)[e]		8 (9.5)	.33
General anesthetics		8 (9.5)[f]		4 (4.8)	.13
NSAID		8 (9.5)[g]		1 (1.2)	.008
Corticosteroids		5 (6.0)[e]		2 (2.4)	.16
Local anesthetics		1 (1.2)[h]		4 (4.8)	.23
PPI		2 (2.4)[g]		2 (2.4)	.64
RCM		2 (2.4)[g]		0 (0.0)	.21
Other		5 (6.0)[e]		2 (2.4)	.15

Abbreviations: ACEI, angiotensin-converting enzyme inhibitors; ARAII, angiotensin II receptor antagonists; ßL, beta-lactam; IQR, interquartile range; NSAID, nonsteroidal anti-inflammatory drugs; PPI, proton pump inhibitors; RCM, radiocontrast media; Δ reaction- study, the interval of time between reaction and study.
Bold values indicate results with statistical significance.
[a]Cause other than drug allergy.
[b]Owing to 57% of cells having n less than 5.
[c]Asymmetric variables are represented as median; thus, apparently, similar displayed values indicate different data.
[d]A total of 28 confirmed.
[e]Only 1 confirmed.
[f]A total of 3 confirmed.
[g]A total of 2 confirmed.
[h]None confirmed.

confirmed drug allergy group and 6 in the excluded drug allergy group (*P* = .30).

Type of Reaction, Severity, and Clinical Manifestations

Analyzing the group of patients with confirmed drug allergy according to the clinical aspects of the reaction, we found that the subgroup of patients with immediate reactions exhibited significantly higher obesity-related parameters than patients with nonimmediate/unknown reactions (Table 3): BMI (*P* = .03), WC (*P* = .049), HC (*P* = .03), BFP (*P* = .01), trunk fat mass and percentage (*P* = .04), leptin (*P* = .04), and leptin-adiponectin ratio (*P* = .02).

No significant differences were found in any of the assessed parameters taking into account the severity of reactions (Table 4) or clinical manifestations (Table 5).

Predictors of Drug Allergy

Logistic regression was performed for the identification of variables that could predict drug allergy (Table 6). The higher the number

Table 2
Anthropometric Measures, Body Composition, Adipokines Levels, Biochemical Parameters, and Other Parameters

Assessed parameters	Confirmed drug allergy (n = 39)	Excluded drug allergy (n = 45)	*P* value
BMI (kg/m^2), mean (SD)	27.3 (4.8)	24.8 (4.6)	**.02**
Weight (kg), mean (SD)	74.3 (15.1)	66.6 (14.6)	**.02**
Waist circumference (cm), mean (SD)	88.3 (13.0)	82.1 (12.3)	**.03**
Hip circumference (cm), mean (SD)	105.3 (11.6)	99.9 (9.0)	**.02**
Waist/hip, mean (SD)	0.96 (0.07)	0.89 (0.06)	**<.001**
Fat mass, mean (SD)	25.9 (9.6)	19.0 (8.9)	**.001**
Body fat percentage (%), mean (SD)	34.6 (8.9)	27.7 (9.8)	**.002**
Trunk fat mass (kg), mean (SD)	13.4 (4.9)	9.7 (4.7)	**.001**
Trunk fat percentage (%), median (IQR)	36.3 (32.2-39.8)	29.8 (21.5-36.9)	**.004**
Fat-free mass (%), median (IQR)	44.3 (40.8-47.6)	44.5 (41.1-54.5)	.93
Lean mass (kg), median (IQR)	24.3 (22.2-26.3)	24.5 (22.3-30.9)	.86
Total body water (kg), median (IQR)	32.6 (29.9-34.8)	32.6 (30.1-39.9)	.92
BMR (kcal), median (IQR)	1328.0 (1253.5-1399.5)	1330.0 (1258.5-1548)	.94
Leptin (ng/mL), mean (SD)	2.87 (1.80)	1.87 (1.64)	**.009**
Adiponectin (ng/mL), mean (SD)	12.57 (4.84)	11.79 (4.47)	.45
Ratio leptin/adiponectin, median (IQR)	0.219 (0.14-0.32)	0.109 (0.05-0.22)	**.005**
Total cholesterol (mg/dL), mean (SD)	191.7 (29.1)	183.1 (34.8)	.24
HDL cholesterol (mg/dL), mean (SD)	56.6 (12.4)	55.5 (13.2)	.70
LDL cholesterol (mg/dL), mean (SD)	115.5 (23.7)	111.6 (29.4)	.53
Triglycerides (mg/dL), median (IQR)	95.0 (60.0-123.0)	79.0 (60.7-113.0)	.42
Glucose (mg/dL), mean (SD)	83.9 (11.8)	81.6 (11.2)	.38
Systolic BP (mm Hg), mean (SD)	125.9 (13.2)	119.7 (16.4)	.08
Diastolic BP (mm Hg), mean (SD)	76.1 (9.0)	73.4 (10.3)	.24
Sleep hours, mean (SD)	7.0 (1.4)	6.8 (1.2)	.48
Number meals per day, mean (SD)	4.4 (1.4)	4.8 (1.0)	.09

Abbreviations: BMI, body mass index; BMR, basal metabolism rate; BP, blood pressure; HDL, high-density lipoprotein; IQR, interquartile range; LDL, low-density lipoprotein.
Bold values indicate results with statistical significance.

Table 3
Patients With Drug Allergy: Results According to the Type of Reaction

Assessed parameters	Immediate reactions (n = 28)	Nonimmediate reactions (n = 11)	*P* value
Age (y), mean (SD)	43.1 (14.1)	35.5 (12.4)	.12
Sex			
Female (n)	23	8	.40
Male (n)	5	3	
BMI (kg/m^2), mean (SD)	28.3 (4.5)	24.7 (4.7)	**.03**
Weight (kg), mean (SD)	75.3 (13.0)	72.0 (19.7)	.59
Waist circumference (cm), mean (SD)	90.9 (11.9)	81.8 (13.7)	**.049**
Hip circumference (cm), mean (SD)	107.9 (9.8)	99.0 (13.8)	**.03**
Waist/hip, mean (SD)	0.97 (0.06)	0.92 (0.08)	.06
Fat mass, mean (SD)	27.9 (8.9)	21.2 (10.1)	.05
Body fat percentage (%), mean (SD)	37.0 (7.9)	29.0 (9.1)	**.01**
Trunk fat mass (kg), mean (SD)	14.5 (4.9)	10.9 (5.3)	**.04**
Trunk fat percentage (%), median (IQR)	38.1 (34.0-42.7)	34.5 (19.3-39.1)	**.04**
Fat-free mass (%), median (IQR)	44.3 (40.9-47.3)	44.7 (40.0-71.8)	.55
Lean mass (kg), median (IQR)	24.1 (22.3-26.1)	24.4 (21.5-40.8)	.68
Total body water (kg), median (IQR)	32.5 (30.0-34.6)	32.6 (30.1-39.9)	.56
BMR (kcal), median (IQR)	1326.0 (1255.3-1392.8)	1335.0 (1234.0-1921.0)	.54
Leptin (ng/mL), mean (SD)	3.24 (1.86)	1.95 (1.27)	**.04**
Adiponectin (ng/mL), mean (SD)	12.38 (5.15)	13.03 (4.18)	.72
Ratio leptin/adiponectin, median (IQR)	0.232 (0.168-0.386)	0.156 (0.630-0.264)	**.02**
Total cholesterol (mg/dL), mean (SD)	193.6 (29.3)	187.1 (29.4)	.54
HDL cholesterol (mg/dL), mean (SD)	57.1 (12.9)	55.6 (11.4)	.74
LDL cholesterol (mg/dL), mean (SD)	114.8 (24.4)	117.5 (23.1)	.76
Triglycerides (mg/dL), median (IQR)	99.5 (66.0-127.0)	63.0 (54.0-116.0)	.19
Glucose (mg/dL), mean (SD)	85.9 (12.6)	78.9 (8.2)	.10
Systolic BP (mm Hg), mean (SD)	123.3 (13.3)	132.3 (11.3)	.07
Diastolic BP (mm Hg), mean (SD)	75.0 (9.7)	78.6 (6.8)	.30
Metabolic syndrome (n)	8	1	.16
Sleep hours, mean (SD)	6.7 (1.4)	7.6 (1.0)	.07
Number meals per day, mean (SD)	4.5 (1.3)	4.2 (1.5)	.30

Abbreviations: BMI, body mass index; BMR, basal metabolism rate; BP, blood pressure; HDL, high-density lipoprotein; IQR, interquartile range; LDL, low-density lipoprotein.
Bold values indicate results with statistical significance.

Table 4
Patients With Drug Allergy: Results According to the Severity of the Reaction

Assessed parameters	Severe reactions (n = 20)	Mild to moderate reactions (n = 17)	*P* value
Age (y), mean (SD)	42.4 (12.9)	39.8 (15.8)	.59
Sex			
Female (n)	15	14	.45
Male (n)	5	3	
BMI (kg/m^2), mean (SD)	28.2 (4.4)	26.5 (5.5)	.30
Weight (kg), mean (SD)	75.1 (12.4)	74.4 (18.6)	.89
Waist circumference (cm), mean (SD)	90.8 (10.9)	85.6 (15.4)	.25
Hip circumference (cm), mean (SD)	107.1 (8.7)	103.4 (14.8)	.35
Waist/hip, mean (SD)	0.97 (0.06)	0.94 (0.08)	.31
Fat mass, mean (SD)	27.5 (8.6)	24.2 (11.3)	.33
Body fat percentage (%), mean (SD)	36.3 (8.3)	32.2 (9.9)	.19
Trunk fat mass (kg), mean (SD)	14.3 (4.4)	12.3 (5.6)	.24
Trunk fat percentage (%), median (IQR)	38.3 (34.0-42.0)	35.1 (27.0-39.4)	.19
Fat-free mass (%), median (IQR)	44.3 (41.4-47.0)	43.7 (40.2-59.3)	.86
Lean mass (kg), median (IQR)	24.3 (22.4-25.9)	23.8 (21.6-33.8)	.73
Total body water (kg), median (IQR)	32.6 (30.3-34.3)	32.1 (29.3-43.8)	.83
BMR (kcal), median (IQR)	1328.0 (1264.0-1386.0)	1314.0 (1237.0-1650.0)	.83
Leptin (ng/mL), mean (SD)	3.00 (1.78)	2.69 (1.96)	.62
Adiponectin (ng/mL), mean (SD)	11.71 (5.25)	12.67 (3.96)	.54
Ratio leptin/adiponectin, median (IQR)	0.232 (0.187-0.350)	0.196 (0.980-0.325)	.27
Total cholesterol (mg/dL), mean (SD)	188.2 (24.9)	195.7 (34.9)	.46
HDL cholesterol (mg/dL), mean (SD)	56.8 (12.8)	55.8 (12.9)	.81
LDL cholesterol (mg/dL), mean (SD)	109.9 (20.5)	121.7 (27.4)	.17
Triglycerides (mg/dL), median (IQR)	95.0 (58.5-127.0)	98.0 (59.0-128.5)	.99
Glucose (mg/dL), mean (SD)	86.6 (12.7)	81.9 (10.7)	.24
Systolic BP (mm Hg), mean (SD)	125.0 (12.6)	126.4 (14.5)	.77
Diastolic BP (mm Hg), mean (SD)	76.5 (8.5)	75.6 (10.1)	.81
Metabolic syndrome (n)	5	4	.50
Sleep hours, mean (SD)	6.9 (1.3)	7.1 (1.5)	.64
Number meals per day mean (SD)	4.5 (1.4)	4.4 (1.4)	.89

Abbreviations: BMI, body mass index; BMR, basal metabolism rate; BP, blood pressure; HDL, high-density lipoprotein; IQR, interquartile range; LDL, low-density lipoprotein.

Table 5
Patients with Drug Allergy: Results According to Clinical Manifestations

Assessed parameters	Anaphylaxis (n = 18)	Others (n = 20)	*P* value
Age (y), mean (SD)	41.7 (13.4)	40.9 (14.8)	.85
Sex			
Female (n)	13	5	.29
Male (n)	5	3	
BMI (kg/m^2), mean (SD)	27.2 (3.3)	27.4 (6.0)	.93
Weight (kg), mean (SD)	75.4 (11.9)	75.3 (18.0)	.71
Waist circumference (cm), mean (SD)	89.2 (9.5)	87.6 (15.8)	.73
Hip circumference (cm), mean (SD)	105.7 (7.9)	105.0 (14.5)	.85
Waist/hip, mean (SD)	0.95 (0.04)	0.96 (0.09)	.77
Fat mass, mean (SD)	25.5 (6.5)	26.3 (12.2)	.79
Body fat percentage (%), mean (SD)	34.8 (7.2)	34.4 (10.6)	.91
Trunk fat mass (kg), mean (SD)	13.3 (3.2)	13.5 (6.2)	.93
Trunk fat percentage (%), median (IQR)	37.8 (32.5-40.4)	36.3 (27.6-40.1)	.93
Fat-free mass (%), median (IQR)	44.3 (41.2-50.4)	44.3 (40.0-48.3)	.73
Lean mass (kg), median (IQR)	24.3 (22.4-28.0)	24.0 (21.5-26.7)	.64
Total body water (kg), median (IQR)	32.5 (30.2-36.8)	32.6 (29.2-35.4)	.75
BMR (kcal), median (IQR)	1328.0 (1260.0-1458.5)	1326.0 (1234.0-1413.0)	.71
Leptin (ng/mL), mean (SD)	2.73 (1.67)	2.99 (1.99)	.66
Adiponectin (ng/mL), mean (SD)	11.93 (5.19)	12.76 (4.57)	.61
Ratio leptin/adiponectin, median (IQR)	0.227 (0.178-0.270)	0.206 (0.109-0.345)	.71
Total cholesterol (mg/dL), mean (SD)	185.5 (24.6)	197.4 (32.7)	.23
HDL cholesterol (mg/dL), mean (SD)	56.6 (12.5)	56.3 (12.8)	.95
LDL cholesterol (mg/dL), mean (SD)	107.3 (20.3)	122.5 (25.1)	.07
Triglycerides (mg/dL), median (IQR)	87.5 (57.5-131.0)	99.0 (62.5-119.8)	.81
Glucose (mg/dL), mean (SD)	86.4 (13.3)	82.4 (10.3)	.31
Systolic BP (mm Hg), mean (SD)	125.3 (13.4)	126.0 (13.6)	.88
Diastolic BP (mm Hg), mean (SD)	75.9 (8.8)	76.3 (9.6)	.90
Metabolic syndrome (n)	4	5	.55
Sleep hours, mean (SD)	7.0 (1.3)	6.9 (1.5)	.79
Number meals per day, mean (SD)	4.5 (1.4)	4.4 (1.3)	.79

Abbreviations: BMI, body mass index; BMR, basal metabolism rate; BP, blood pressure; HDL, high-density lipoprotein; IQR, interquartile range; LDL, low-density lipoprotein.

Table 6
Predictive Factors of Confirmed Drug Allergy

Variable	OR	95% CI	*P* value
Immediate reactions	3.81[a]	1.30-11.14	**.02**
Number of reactions	2.82[b]	1.31-6.10	**.008**
Body fat percentage	1.07[c]	1.01-1.14	**.02**

Abbreviations: CI, confidence interval; OR, odds ratio.
Bold values indicate results with statistical significance.
NOTE: Included covariables are body mass index and leptin.
[a]Compared with nonimmediate and unknown reactions.
[b]For each increase in the number of reactions.
[c]For each 1 unit increase in the body fat percentage, the OR increases by 1.07.

of reactions and the higher the BFP, the greater the odds of developing drug allergy. An immediate allergic reaction was also a predictor of confirmed drug allergy.

BFP was also a predictor of having an immediate reaction to drugs. Analyzing the patients with confirmed drug allergy, we found that the higher the BFP, the greater the odds of having an immediate drug allergic reaction (Table 7).

Table 7
Predictive Factors of Immediate Drug Allergic Reaction

Variable	OR	95 % CI	*P* value
Body fat percentage[a]	1.12	1.02-1.24	**.02**

Abbreviations: CI, confidence interval; OR, odds ratio.
Bold values indicate results with statistical significance.
NOTE: Included covariables are body mass index, waist circumference, hip circumference, and leptin.
[a]For each 1 unit increase in the body fat percentage, the OR increases by 1.12.

Discussion

To our knowledge, this is the first study investigating a potential link between drug allergy and obesity. Our results highlight that drug allergy is associated with obesity traits, assessed by different measurements. Patients with drug allergy exhibited significantly higher parameters associated with both global obesity and central obesity compared with patients with excluded drug allergy. They also presented higher levels of systemic inflammatory markers such as serum leptin and leptin-adiponectin ratio. No statistical association was found with metabolic parameters, particularly metabolic syndrome. This may probably reflect a strong association of drug allergy with systemic inflammation rather than with metabolic factors.

The finding that obesity generally induces a low-level but chronic and systemic inflammation beyond the metabolic tissues deeply changed the previous concept of obesity as an exclusively metabolic disorder[27] and boosted research in other potential associated diseases. Many studies involved allergic diseases, mainly respiratory diseases, and several correlated these 2 diseases.[8-22] A recent study highlighted the impact of diabetes-associated inflammation on asthma outcomes.[40]

A shift from an anti-inflammatory M2-like to a proinflammatory M1-like macrophage phenotype is considered a main contributor to inflammation in obesity.[25,27,30,41] Although macrophages are an important source of AT inflammation, there is growing evidence that obesity also induces an immune response involving other immune cells of the adaptive and innate system that further aggravates systemic inflammation and contributes to the onset of obesity-associated comorbidities.[25] Numerous changes in T cell subpopulations in the AT also seem to come with the development of obesity,[27] as fewer regulatory T cells (Tregs) and T_H2 cells and a higher frequency of T_H1 and T_H17 cells all hallmarks of a shift from an anti-inflammatory to the proinflammatory milieu.[25,27,41] In contrast, a recent review reported that AT-resident mast cells, under the influence of AT-derived cytokines, become activated and

release proinflammatory cytokines and recruit leukocytes with inflammatory activity.[41] However, the main focus has been AT immune cells,[25] and much of the information comes from murine models.[27]

Great knowledge was achieved in the field of obesity and its comorbidities, but further research is still needed, particularly with respect to allergic diseases. The underlying immunopathologic mechanisms linking the 2 diseases remain unclear, though some possibilities have been proposed based on some evidence. Whereas laboratory studies have indicated that the overall effect of leptin on memory T cells is to increase T_H1 responses and decrease T_H2 responses, many studies point out a role in allergic diseases.[6,8,14,20,23,24,28,29] A recent study found that serum leptin was related to enhanced $T_H2/17$ inflammation and inhibited Treg function in obese children with allergic rhinitis.[20] Interestingly, some authors argue that the increased serum levels of leptin in obesity decrease the proliferation of Treg cells, impairing immunologic tolerance to allergens and promoting allergic sensitization.[6,8,23] One previous study found evidence of a direct relationship between obesity and T_H2 cells in women.[21] Other research found that leptin may promote an allergic response by binding to leptin receptors present in human eosinophils[28] (delaying spontaneous eosinophil apoptosis[28] and increasing chemotaxis and adhesion at high serum levels[14]) and basophils (enhancing migration, survival, CD63 expression, degranulation, and cytokine production at high concentrations).[24]

Besides the statistical association between drug allergy and obesity, our study also suggests that patients with immediate reactions to drugs exhibit significantly higher obesity-related parameters compared with patients with nonimmediate/unknown reactions. No significant differences were found in any of the assessed parameters with respect to the severity of reactions or clinical manifestations.

Moreover, the logistic regression analysis revealed BFP as a predictor of drug allergy and immediate reactions to drugs. The higher the BFP, the greater the odds of developing drug allergy and particularly an immediate reaction to drugs.

These results reveal an association between obesity and immediate reactions to drugs. No statistical associations were found between obesity parameters and the severity of the reactions or clinical manifestations. Taken together, this suggests a type 1, IgE-mediated immune mechanism given that these reactions include a variety of clinical manifestations with varying degrees of severity.

As mentioned above, there are no previous studies investigating a link between drug allergy and obesity. However, some reports[42,43] notice worse outcomes in patients who are obese that underwent an allergic reaction to drugs. The sixth National Audit Project concerning epidemiology and clinical features of perioperative anaphylaxis described that 21% of all patients were obese or morbidly obese.[42] Furthermore, of the 10 cases with fatal outcomes, only 1 patient had normal weight, 4 were overweight and 5 were obese (4 morbidly obese). Another recent study[43] assessed a potential association between serum tryptase concentrations during general anesthesia and the use of neuromuscular blocking agents and BMI. They found that postoperative serum tryptase concentrations were not directly correlated with rocuronium doses but with BMI values, with overweight/obesity predisposing to higher serum tryptase concentrations. These reports support a possible association between obesity and drug allergy, with a type 1 underlying immune mechanism. However, in these cases, a non-IgE mechanism may also be involved because specific drugs like neuromuscular blocking agents can activate mast cells through interaction with MRGPRX2 receptors.[44]

We also found that the allergy diagnostic workup results were different according to the clinical features of the reaction. The number of reactions and the immediate-type reaction were found to be predictors of a positive result. This is a relevant finding because if supported by larger studies, it may lead to changes in the extensive and time-consuming protocols.

In our study, it was important to perform a broad evaluation of obesity, including not only anthropometric measurements but also body composition by bioimpedance. Indeed, BMI is the most widely used method to diagnose obesity but it is quite limited on its own given that it does not provide an accurate measurement of body composition[10,11,25] and it does not seem to correlate with inflammation.[45] It was also relevant to evaluate both the amount of body fat and fat distribution, given that inflammation and obesity-related comorbidities are found to be more closely associated with abdominal adiposity and visceral fat.[25,31,32] The diagnosis of drug allergy was based on a diagnostic workup and the interval of the time between the reaction and the study are other strengths of this study. For some drugs, the sensitivity of the diagnostic workup decreases over time.[5]

Some limitations of our study should be noted. First, the cross-sectional study design does not allow to establish causal associations between obesity and drug allergy. Second, our study did not include all types/subtypes of immune reactions to drugs,[1,2] mainly because some of them are rare. In addition, life-threatening severe cutaneous adverse reactions are extremely severe and the usual in-vivo allergy diagnostic procedures are contraindicated.[46] Moreover, in some patients, it was not possible to classify the reaction according to the underlying immune mechanism. Finally, the sample size of the current study could be considered moderate and 2 main reasons may explain this constraint: one is that drug allergy is not frequently confirmed after a diagnostic workup, and another is that diagnostic procedures take a significant time until final diagnosis in a prospective study like ours.

Obesity has been the focus of intense research and its prevalence has reached epidemic proportions with well-known associated diseases and complications. We identified drug allergy as a potential new player in this scenario. Allergic reactions to drugs are usually unpredictable and they can be very complex and severe, even life-threatening. Wider knowledge of their risk factors especially those potentially modified by lifestyle interventions may have a significant impact on susceptible individuals.

In conclusion, our study illustrates, for the first time, evidence of a link between obesity and drug allergy, particularly with immediate reactions. BFP emerged as a potential predictor of drug allergy. Further studies are needed to clarify and confirm this association and its underlying immunopathologic mechanisms. This is a priority topic that may lead to new approaches in the field of drug allergy. Multidisciplinary teams composed of allergists, endocrinologists, and nutritionists should work together to improve systemic inflammatory/metabolic parameters and modify drug allergy outcomes.

Acknowledgment

The authors thank Alice Cortez (Department of Biomedicine, Faculty of Medicine, University of Porto) for her technical assistance in leptin and adiponectin assays.

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Dietary parameters in patients with drug allergy: assessing dietary inflammatory index

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Conflicts of interest: The authors declare that they have no conflicts of interest.

Abstract

Background: The low-grade systemic inflammation related to obesity is associated with several diseases and can be modulated by diet. Research on the increasing incidence of allergic diseases evidenced the role of diet as a potential key factor.

Aim: To investigate a potential association between diet, including dietary inflammatory index (DII), and drug allergy. Also, to evaluate correlations between diet and obesity, inflammatory and metabolic parameters in patients with drug allergy.

Methods: Ninety consecutive patients studied for suspected drug allergy were evaluated in terms of dietary parameters, anthropometric measurements, bioimpedance and biochemical analysis. DII was calculated based on information collected from a food frequency questionnaire.

Results: After diagnostic work-up, 39 patients had confirmed drug allergy and 45 excluded, representing the study group and the control group, respectively. The majority (79%) were female, with mean age of 39.58±13.3 years. The 84 subjects revealed an anti-inflammatory diet pattern. No significative difference was found in DII scores between drug allergic patients and controls (-3.37±0.95 vs -3.39±0.86, p= 0.985). However, patients with drug allergy revealed higher obesity and inflammatory parameters.

A significative negative correlation was found between DII and adiponectin levels, in the control group (r=-0.311, p=0.040). In the patients group, a significative positive correlation was observed between DII and triglycerides (r=0.359, p=0.032). No other correlations were found between DII and the assessed parameters.

Patients with drug allergy presented a significative higher intake of mono-unsaturated fatty-acids comparing to controls (19.8±3.7 vs 17.8 ± 4.0, p= 0.021). No other statistically significant differences were achieved in dietary parameters, between patients and controls.

Conclusion: Our population revealed an anti-inflammatory diet profile. Although patients with drug allergy revealed higher obesity and inflammatory parameters, the DII did not allow to distinguish between patients with drug allergy or controls. The DII scores correlated with triglycerides levels in the drug allergy patients and inversely with adiponectin levels in the control group.

Larger studies are needed to clarify the potential role of the diet in drug allergy and its outcomes.

Key words:
Drug hypersensitivity
Dietary inflammatory index
Macronutrients
Micronutrients
Inflammation
Obesity

Abbreviations:
DII- dietary inflammatory index
ADR- adverse drug reaction
ENDA- European Network of Drug Allergy
IPAQ- Intensity Physical Activity Questionnaire
DPT- drug provocation test
FFQ- food frequency questionnaire
BMI- body mass index
WC- waist circumference
IDF- International Diabetes Federation
HP- hip circumference
WHR- waist-hip ratio
HDL- high-density lipoprotein
LDL- low-density lipoprotein
BFP- body fat percentage
MUFA- mono-unsaturated fatty acid
PUFA- polyunsaturated fatty acid
SFA- saturated fatty-acid
SD- standard deviation
IQR- interquartile range
BP- blood pressure

1 – Introduction

Obesity has become epidemic [1] and a major public health problem in the developed world [2-3]. Much of the disease risk is related to the associated low-grade systemic inflammation [1-5]. As visceral fat has a more proinflammatory secretory profile than subcutaneous fat, central obesity is particularly relevant [2,5].

Low-grade chronic inflammation has been associated with several chronic conditions and can be modulated by diet [6-9]. While polyunsaturated fatty acids and antioxidant vitamins have shown a protective role [6,8,10-11] , total fat and saturate fat acids revealed pro-inflammatory properties [6,8,11].

A dietary pattern approach has been considered advantageous since it considers the combined and interacting effects of nutrients and other food components [7,12].

The dietary inflammatory index (DII) is a tool, developed by Cavicchia[6] and updated by Shivappa [7], that measures the inflammatory potential of the diet, from maximally anti-inflammatory to maximally pro-inflammatory. The purpose was to be used across diverse population in order to predict inflammatory levels and related health outcomes [8]. It has been used in several studies and chronic diseases [13-19] like metabolic [8] and cardiovascular diseases [14,15], but also in asthma [17-19].

Research on the increasing incidence of asthma and other allergic diseases evidenced the role of diet as a potential key factor influencing immune homeostasis through a complex interplay between nutrients, their metabolites and immune cell populations [20].

Allergic drug reactions are unpredictable adverse drug reactions (ADR) that are mediated by an immunological mechanism [21-22]. These reactions are usually classified according the underlying mechanism [22-24], but also based on the time of the onset [22]. Several manifestations with different degrees of severity can occur [22-24]. Although it is estimated that drug allergy accounts for less than 10% of all ADR [25], its incidence increased in line with the overall increase in the incidence of allergic diseases [21].

2- Aim

The main purpose of this study was to investigate a potential association between diet, including dietary inflammatory index, and drug allergy.

It was also our aim to evaluate correlations between dietary parameters and obesity, inflammatory and metabolic parameters, in drug allergic patients.

3 –Methods:

Study Population:

Ninety consecutive adult patients with a suggestive history of drug allergy in the previous five years were prospectively studied in our Department, from September 2017 to October 2018. A complete history based on a validated questionnaire (the drug hypersensitivity questionnaire developed by European Network of Drug Allergy- ENDA) [26]. was obtained in the outpatient clinic. Patients were invited to participate by phone the day before their first visit to the day hospital. The patient inclusion process is outlined in a previous publication [27].

Social-demographic data were collected.

Leisure-time physical activity was evaluated through two questions about the type of exercise and the time spend on it in a week (number of hours) and classified in intensity categories (sedentary, irregularly active, active and intensely active), considering the 4 categories of the Intensity Physical Activity Questionnaire (IPAQ) classification [28].

The protocol was approved by the Hospital Ethics Committee (CE-66-2016) and written informed consent was obtained from all participants included in the study.

Drug allergy diagnostic work-up:

The diagnostic work-up was performed considering clinical history and according to international guidelines [22]. It included skin tests [29-30], specific IgE and drug provocation tests (DPT) [31].

The diagnosis of drug allergy was confirmed when skin tests were positive for validated concentrations or when specific provocation test with the suspected drug was positive. If all diagnostic procedures were negative, including DPT with the suspected drug, drug allergy was excluded. Patients that did not complete the allergy diagnostic protocol or that did not have a conclusive diagnosis were excluded.

Dietary inflammatory index (DII)

The Dietary inflammatory Index (DII) score is a calculated parameter that provides an estimate of the inflammatory potential of the diet. An individual's diet is considered more pro-inflammatory when the DII score is more positive, while the diet is considered more anti-inflammatory when the DII score is more negative. The DII score was calculated according to Shivappa *et al* [7]. and categorizes a list with 45 possible food items, which range from maximally anti-inflammatory to maximally pro-inflammatory potential.

Dietary data were obtained from a 91-item self-administered and semi-quantitative food-frequency questionnaire validated (FFQ) for Portuguese population [32]. This questionnaire was applied indirectly by a nutritionist to all participants allowing to assess the eating habits related to the previous 12 months. Dietary intake estimation was made multiplying the portion size in grams by the multiple fraction of daily frequency intake and by a seasonality variation factor. The conversion, from food to energy and nutrients intake, was performed using The Food Processor Plus program version SQL (ESHA Research, Salem, OR, USA). This database was supplemented with the Portuguese food composition database [33].

The DII score was calculated considering 28 of 45 possible food parameters. Data on β-carotene, eugenol, garlic, ginger, onion, saffron, turmeric, pepper, green/black tea, thyme/oregano, rosemary, flavan-3-ol, flavones, flavonols, flavonones, isoflavones and anthocyanidis, were not included since no information was available for these components in the Food Processor nutritional database.

To derive the individual DII scores, the global average intake (taken from Shivappa et al [7]) was subtracted from the reported daily intake of each nutrient in the FFQ and divided by the standard deviation of the global daily intake, rendering a z-score which was converted into a centered percentile score. This score was then multiplied with an overall inflammatory effect score. All 28 parameters included individually calculated nutrient-specific effect scores were then summed to obtain the global DII score.

Anthropometric measurements and body composition

Height (to the nearest 0.5 cm) and body weight (to the nearest 0.1 kg) were measured with patients wearing light clothing and no shoes.

Body mass index (BMI) was calculated by dividing weight by squared height. According to the BMI categories defined by World Health Organization guidelines, patients were classified as normal weight (≥18.5 and < 25 $kg.m^{-2}$); overweight (≥ 25.0 and <30 $kg.m^{-2}$) and obese (≥30.0 $kg.m^{-2}$) [34].

Waist circumference (WC) was measured at the level midway between the lowest rib and the iliac crest. Based on International Diabetes Federation (IDF) criteria, central obesity was defined as WC ≥0.80 m in women and ≥0.94 m in men [35-36]. Hip circumference (HC) was measured at the level of the widest circumference over the great trochanters. Both circumferences were measured with a flexible tap with subjects standing at the end of gentle expiration. The waist-hip ratio (WHR) was calculated[34].

Body composition, including fat mass (Kg and percentage), was assessed by bioimpedance (*Inbody 230*, Body Composition Analyzer; tetra polar 8-point tactile electrodes, BIOSPACE).

Biochemical analysis

Serum leptin and serum adiponectin concentration were measured with the double antibody sandwich ELISA assay by using an antibody specific for human leptin and for human adiponectin, respectively (Mercodia Leptin ELISA/Mercodia Adiponectin, Mercodia AB, Uppsala, Sweden). Blood samples were obtained after overnight fasting, between 8 and 9 am. After clotting at 4ºC, serum was separated by centrifugation and stored at – 70º until assay.

Blood samples for glucose, total cholesterol, high-density lipoprotein (HDL) and triglycerides in serum were obtained, at the same time using anticoagulant-treated tubes and their concentrations determined by standard techniques. The low-density lipoprotein (LDL) levels were calculated according to the manufacturer's instructions (Roche, Rotkreuz, Switzerland).

Statistical analysis:

The statistical Package for Social Sciences® version 25 was used to analyze data and statistical significance was defined as $p < 0.05$.

For continuous quantitative variables, the existence of normal distribution was tested through histogram observation, kurtosis and skewness analysis and using the Kolmogorov-Smirnov test. To describe these variables, central tendency measures (mean and median) and dispersion measures (standard-deviation and percentiles 25-75) were used. To compare continuous variables with normal and non-normal distribution between two groups, an Independent Samples t Test and a Mann Whitney test were used, respectively. To compare continuous variables with normal and non-normal distribution between more than two groups, an ANOVA with Bonferroni correction and a Kruskal-Wallis test were used, respectively. For qualitative variables we used absolute numbers and percentages. To analyze differences between groups in categorical variables, the chi-square test and the Fisher exact test were used. Correlations were evaluated using the Pearson and the Spearman correlation tests for continuous symmetrical and asymmetrical variables, respectively.

3 –Results:

Study population

Eighty-four patients completed the drug allergy diagnostic work-up with a conclusive result: 39 patients (46%) had the final diagnosis of confirmed drug allergy and in 45 (54%) drug allergy was excluded, representing the study group and the control group, respectively.

Seventy-nine per cent of the patients were female and the mean age was 39.58 ± 13.3 years, range [18 - 77].

The two groups were homogeneous concerning socio-demographic and general clinical characteristics. There were significative differences concerning the drug allergic reactions between the two groups. Details are presented in a previous publication [27].

Regarding BMI, 42.2% of patients had normal weight, 36% were overweight, 19.3% obese and 2.4% underweight. According to the IDF criteria, 57.6% of the women and 41.2% of the men presented central obesity. Patients with drug allergy revealed significantly higher obesity-related parameters than controls (results detailed in our previous study) [27].

Dietary inflammatory index (DII) and drug allergy

Globally, the 84 subjects revealed an anti-inflammatory diet pattern with a mean DII of -3.38 ± 0.9 (min -4.66, max -0.93).

No significative differences were found in DII scores between patients with confirmed drug allergy and controls (-3.37 ± 0.95 vs -3.39 ± 0.86, p= 0.985).

Analyzing the 39 patients with confirmed drug allergy, no differences were observed in DII scores regarding the clinical manifestations, the type or the severity of the reactions (table 1).

Dietary inflammatory index (DII) and obesity parameters

There were no significant correlations between DII scores and anthropometric measurements or body composition by bioimpedance analyzed as continues variables, neither in the globality of the evaluated individuals, nor in the patient group or in the control group (table 2).

Dietary inflammatory index (DII) adipokines levels, biochemical and other parameters

With respect to adipokines levels, a significative and negative correlation was found between DII and adiponectin levels, when all the individuals (r=-0.254, p=0.021) and the control group (r=-0.311, p=0.040) were considered, but not the drug allergy group (r=-0.225, p=0.175) (table 3). Regarding the other assessed parameters, including biochemical parameters, no significant correlations were observed with DII, except for triglycerides in the drug allergic group (r=0.359, p=0.032) (table 3).

Macronutrients, micronutrients and drug allergy

In tables 4 and 5 the dietary parameters are described according to macronutrients and micronutrients, respectively. We found that the drug allergic patients presented a significantly

higher intake of mono-unsaturated fatty-acids (MUFA) compared to controls (19.8 ± 3.7 vs 17.8 ± 4.0, p= 0.021). No other statistically significant differences were observed.

Physical activity and obesity, biochemical and other parameters

In terms of physical activity, the majority of individuals (48.8%) were sedentary, 26.2% irregularly active, 9.5% active and 14.3% intensely active. In the group of patients with drug allergy, 21 (53.8%) were classified as sedentary, 9 (23.1%) irregularly active, 4 (10.3%) active and 4 (10.3%) intensely active, while 8 controls (17.8%) were intensely active, 4 (8.9%) active, 13 (28.9%) irregularly active and 20 (44.4%) sedentary.

No differences with statistical significance were obtained between the 4 categories of physical activity regarding anthropometric/ bioimpedance, inflammatory and biochemical parameters assessed or with the DII scores.

4 –Discussion:

To our knowledge, this is the first study applying the DII score in the assessment of patients with drug allergy. We found a slightly higher DII score in patients with drug allergy compared to controls but not achieving statistical significance. Nonetheless, the former group revealed significantly higher obesity parameters and leptin levels, as detailed elsewhere [27]. This result can be in part related to the general dietary pattern of our sample, but also to the sample size. Interestingly, the globality of the individuals of our study presented an anti-inflammatory DII (DII= -3.38), suggesting a Mediterranean diet pattern [20]. This DII score is considerably more anti-inflammatory than the few studies involving patients with asthma, performed in Australia [18] (DII asthma group=−1.40±0.2; controls=−1.86±0.4, p=0.04), in Portugal [19] (0.1 ± 1.5) and in EUA [17] (DII scores revealed a pro-inflammatory diet in all evaluated groups). Other studies carried out in our country also showed higher DII scores, particularly studies involving children [19,37] or adolescents [13], but also adults (-0.35 ± 1.88) [38]. These differences might also reflect regional and age differences in dietary patterns.

In our study, no significant correlations were found between DII scores and obesity parameters assessed by anthropometric measurements or by bioimpedance. In very large sample studies, individuals with higher pro-inflammatory diets assessed by DII presented higher obesity parameters, such as BMI [14,39-40] and especially waist circumference [14]. With these results the authors discuss that a pro-inflammatory diet might contribute to increase or maintain obesity, especially abdominal obesity, in a population mostly overweight or obese [14]. It is well established that the link between obesity and diet is not exclusively related to the balance

297 between energy intake and expenditure [20], but also with the inflammatory pattern of the diet
298 and its potential to modulate the low-grade chronic inflammation state associated with obesity
299 [6-9]. Several studies investigated and found associations between DII scores and
300 inflammatory systemic markers, as CRP [8,42], TNF-alfa [16,42], IL6 [13,17], C3 [13,42], and
301 also with biochemical parameters as triglycerides [41-42], and other lipoproteins [41].
302 Within the inflammatory and biochemical parameters assessed in our study, we found a
303 negative correlation between the DII scores and adiponectin levels, when all the individuals or
304 only the control group were considered. This correlation was not present in the drug allergy
305 group. Adiponectin is an anti-inflammatory adipokine that is downregulated in the obesity
306 status[43]. A negative correlation with DII scores means that patients with higher DII scores
307 or more anti-inflammatory diet, have lower adiponectin serum levels which is in accordance
308 with the adiponectin role and with other studies [41]. Moreover, this correlation was observed
309 in the control group, with less obesity parameters and leptin levels [27], but not in the drug
310 allergic patients. We also observed a positive correlation between DII scores and triglycerides
311 levels exclusively in the drug allergic group, illustrating that patients with a less anti-
312 inflammatory diet have higher triglycerides levels. Also, this correlation was only present in
313 the group with higher obesity parameters and systemic inflammatory parameters [27].
314 With respect to individual macro and micronutrients and other food components, we did not
315 find any association with drug allergy, except for MUFAs, with higher intake in this group
316 compared to controls. This is an unexpected result, as MUFAs have globally shown anti-
317 inflammatory effects [44]. Moreover, this result does not take into account the whole diet and
318 the interaction between its components, and a dietary pattern approach is more appropriate
319 [7,12,44-45]. Although, Heinrich *et al*, in 2001, used the European Community Respiratory
320 Health Survey (ECRHS) that included 3,872 subjects, and concluded that a high intake of
321 MUFAs might promote the development of allergic sensitization [46].
322 In terms of the potential role of the diet and its components in the development of allergic
323 diseases and its outcomes, research is focused not only in dietary patterns [17-19, 43,45], but
324 also in individual nutrients and food components, [47-49] and their potential influence
325 throughout life, including in fetal life[50]. Although some results are inconsistent, there is
326 evidence that the Mediterranean diet pattern has a protective role[2] [20,44-45,47] and a Western
327 diet pattern a deleterious one [20,44]. This is mostly attributed to the high content in
328 antioxidants, fibers, polyunsaturated fatty-acids omega-3 (w3-PUFAs) and MUFAs of the
329 Mediterranean diet, combined with low amounts of saturated fatty-acids (SFAs) [20,44-45,47].
330 Conversely, the Western diet is a high caloric diet, rich in SAFs and w-6 PUFAs, and with low

intake of w-3 PUFAs, fiber and antioxidants [20,44-45,47]. The role of individual nutrients and other food components is not yet clearly established in allergic diseases, although several have revealed potential effects. The ratio w3-PUFAs/w-6 PUFAs might be important [44-45,49], while fruits and vegetables have revealed to have the most consistent protective effects[42,44,47-48], probably because they are rich in antioxidants such as vitamin C, E and β-carotene and also in flavonoids, isoflavonoids and polyphenolic compounds [45,48]. On the other hand, vitamin A and D deficiency might influence the development of allergy and its outcomes [20,47].

Physical activity was also evaluated in this study, as exercise has demonstrated an effect on total and abdominal adiposity [51], serum adipokines [52] and biochemical parameters[53].

No statistically significant differences were found between the 4 categories of physical activity regarding anthropometric/ bioimpedance, inflammatory and biochemical parameters evaluated, probably due to the reduced number of individuals in each category. We also analysed a potential association between physical activity and DII scores, as both may reflect a certain type of lifestyle, but also here the sample size might have influenced the absence of a significant association.

The global anti-inflammatory diet pattern of our sample might represent a constraint to the results of our study. Other limitations of our study also deserve consideration. First, the sample size also did not allow the analysis according to the standardized terciles or quartiles as seen in other studies. Second, 14 nutrients/components were not included in the DII assessment, as no data was available in the Portuguese food composition database. Third, dietary habits were collected using self-reported information from FFQs and based on patients recall from the last 12 months. However, the use of a validated FFQ is considered an appropriate tool for this purpose and permits seasonality intake. This is not possible with 24h-Food questionnaires but, on the other hand, these questionnaires are more specific and do not have recall bias. Fourth, a trained nutritionist assisted the participants in our study. This fact could avoid some inaccuracies, but could also influence patients´ answers, as they tend to respond according to social desirability [54]. Finally, the method used for the evaluation of physical activity was not based on objective measures and the question of the social desirability may also have influenced the patients´ answers.

On the other hand, the prospective design, the high number of dietary parameters evaluated, the global assessment of obesity parameters, the assessment of a considerable number of potential confounders and drug-allergy work-up were relevant in our study.

5- Conclusions:

Our population revealed an anti-inflammatory diet profile. Although patients with drug allergy revealed higher obesity and inflammatory parameters, the DII did not allow to distinguish between patients with drug allergy and controls. However, the DII scores correlated with triglycerides levels in drug allergic patients and inversely with adiponectin levels in the control group.

Larger studies are needed to clarify the potential role of the diet in drug allergy and its outcomes.

Table 1. Patients with drug allergy: DII scores and characteristics of the reaction

	DII score	P value
Type of reaction		
Immediate reactions, Median (IQR)	-3.58 [(-4.03) - (-3.01)]	0.751
Non-immediate reactions, Median (IQR)	-3.21 [(-4.23) - (-2.72)]	
Severity of reaction		
Severe reactions, Median (IQR)	-3.40 [(-4.00) - (-3.05)]	0.975
Mild/moderate reactions, Median (IQR)	-3.57 [(-4.11) - (-2.73)]	
Anaphylaxis		
Yes, Median (IQR)	-3.32 [(-4.03) - (-3.00)]	0.729
No, Median (IQR)	-3.64 [(-4.15) - (2.74)]	
MPE		
Yes, Median (IQR)	-3.21 [(-4.54) - (-1.60)]	0.894
No, Median (IQR)	-3.58 [(-4.00) - (-3.02)]	

IQR- interquartile range, MPE- maculopapular exanthema

Table 2. Correlations between DII and anthropometric/bioimpedance parameters

DII	**All individuals (n=84)**		**Drug allergy group(n=39)**		**Control group(n=45)**	
	R value	**P value**	**R value**	**P value**	**R value**	**P value**
BMI (kg/m-^{2})	0.096	0.387	0.111	0.507	0.086	0.575
Waist circumference (cm)	0.070	0.528	0.040	0.813	0.098	0.524
Hip circumference (cm)	0.072	0.517	0.117	0.483	0.001	0.997
Waist/Hip	-0.012	0.911	-0.038	0.820	0.013	0.932
Fat mass (kg)	0.009	0.940	-0.011	0.949	-0.004	0.981
Body fat percentage (%)	-0.038	0.739	-0.063	0.711	-0.028	0.854
Trunk fat mass (kg)	0.015	0.894	-0.003	0.986	-0.012	0.938
Trunk fat percentage (%)	-0.34	0.761	-0.056	0.742	-0.029	0.854
Trunk lean mass (kg)	0.126	0.262	0.141	0.404	0.104	0.500
Fat free mass (%)	0.115	0.307	0.145	0.391	0.113	0.465
Lean mass (kg)	0.122	0.278	0.153	0.365	0.128	0.408

BMI-Body mass index; BMR- Basal metabolism rate;
All variables were analyzed as continues

Table 3. Correlations between DII and adipokines levels, biochemical parameters and other parameters

DII	All individuals (n=84)		Drug allergy group (n=39)		Control Group (n=45)	
DII	**R value**	**P value**	**R value**	**P value**	**R value**	**P value**
Leptin (ng/ml)	-0.107	0.334	-0.078	0.643	-0.157	0.305
Adiponectin (ng/ml)	**-0.254**	**0.021**	-0.225	0.175	**-0.311**	**0.040**
Ratio leptin/adiponectin	0.006	0.954	0.082	0.626	-0.057	0.060
Total cholesterol (mg/dl)	-0.065	0.568	-0.068	0.689	-0.064	0.686
HDL cholesterol (mg/dl)	-0.188	0.097	-0.301	0.070	-0.088	0.577
LDL cholesterol (mg/dl)	-0.001	0.994	-0.011	0.951	-0.012	0.942
Triglycerides (mg/dl)	0.138	0.229	**0.359**	**0.032**	-0.084	0.596
Glucose (mg/dl)	0.053	0.643	0.174	0.302	-0.095	0.556
Systolic BP (mmHg)	0.025	0.829	-0.051	0.775	0.024	0.880
Diastolic BP (mmHg)	0.010	0.932	0.095	0.595	-0.080	0.616

HDL-high-density lipoprotein; LDL- low-density lipoprotein; BP- Blood pressure

Table 4. Macronutrients intake and drug allergy diagnosis

	Confirmed drug allergy (N=38)	Excluded drug allergy (N=45)	P value
Calories (kcal), Mean (SD)	2457.3 (648.7)	2488.7 (550.7)	0.812
Protein (g), Mean (SD)	111.2 (32.4)	113.6 (25.1)	0.697
Carbohydrates (g), Mean (SD)	266.8 (74.8)	284.6 (79.2)	0.298
Fibre (g), Mean (SD)	31.0 (11.7)	31.2 (11.3)	0.914
Total fat (g), Mean (SD)	106.4 (31.5)	101.3 (26.1)	0.418
Cholesterol (mg), Mean (SD)	349.3 (109.8)	338.1 (92.3)	0.616
Linolenic acid(g), Median (IQR)	1.4 (1.1 – 1.7)	1.3 (1.1 – 1.8)	0.877
Trans fat (g), Median (IQR)	0.9 (0.7 – 1.2)	0.9 (0.7 – 1.1)	0.844
Sodium (mg), Mean (SD)	2112.3 (696.0)	2228.5 (608.9)	0.419
Water (%), Mean (SD)	1573.5 (515.4)	1626.8 (461.9)	0.621
Alcohol (g), Median (IQR)	1.7 (0.0 – 5.2)	1.7 (0.0 – 10.9)	0.464
Caffeine (mg), Median (IQR)	81.3 (31.4 – 105.1)	78.8 (19.2 – 86.4)	0.187
Protein (TEV), Mean (SD)	18.0 (2.0)	18.3 (2.2)	0.477
Carbohydrates (TEV), Mean (SD)	43.7 (7.2)	45.5 (5.5)	0.191
Simple sugars (TEV), Mean (SD)	18.1 (4.8)	19.4 (4.3)	0.178
Total fat (TEV), Mean (SD)	38.9 (5.3)	36.6 (5.5)	0.060
Polyunsaturated fat (TEV), Mean (SD)	6.5 (0.9)	6.3 (1.2)	0.695
Omega-3 (TEV), Mean (SD)	0.6 (0.1)	0.6 (0.1)	0.593
Omega-6 (TEV), Mean (SD)	5.2 (1.0)	5.1 (1.2)	0.558
Saturated fat (TEV), Mean (SD)	9.6 (1.7)	9.5 (1.5)	0.820
Linoleic acid (TEV), Mean (SD)	5.0 (1.0)	4.9 (1.2)	0.523
Monounsaturated fat (TEV), Mean (SD)	**19.8 (3.7)**	**17.8 (4.0)**	**0.021**
Linolenic acid(TEV), Median (IQR)	12.9 (9.9 – 15.4)	12.0 (10.0 – 16.0)	0.913
Trans fat (TEV), Median (IQR)	0.3 (0.3 –0.5)	0.3 (0.3 –0.4)	0.777
Ethanol (TEV), Median (IQR)	11.6 (0.0 – 36.2)	11.6 (0.0 – 76.3)	0.409

SD- standard deviation; IQR- interquartile range; TEV-total energy value

Table 5. Micronutrients intake and drug allergy diagnosis

	Confirmed drug allergy (N=38)	**Excluded drug allergy** (N=45)	**P value**
Vitamin A (RE), Mean (SD)	2313.2 (1183.1)	2483.5 (1342.0)	0.485
Niacin B3 (mg), Mean (SD)	26.2 (7.3)	28.6 (8.6)	0.625
Folate (mcg), Mean (SD)	418.7 (171.2)	420.4 (177.0)	0.890
Iron (mg), Mean (SD)	17.7 (4.9)	18.8 (6.2)	0.371
Magnesium (mg), Mean (SD)	418.4 (147.6)	408.6 (120.8)	0.166
Potassium (mg), Mean (SD)	4009.5 (1287.4)	4194.5 (1092.6)	0.496
Selenium (mg), Mean (SD)	121.1 (40.1)	117.1 (33.9)	0.173
Zinc (mg), Mean (SD)	13.5 (4.3)	14.0 (3.9)	0.231
Vitamin D (mcg), Mean (SD)	4.7 (2.0)	5.1 (2.0)	0.919
Vitamin E (mg), Mean (SD)	14.4 (4.4)	14.0 (4.4)	0.936
Thiamine B1 (mg), Median (IQR)	1.7 (1.5 – 2.1)	1.8 (1.5 – 2.2)	0.285
Riboflavin B2 (mg), Median (IQR)	2.1 (1.7 – 2.6)	2.2 (1.8 – 2.7)	0.344
Vitamin B6 (mg), Median (IQR)	2.3 (2.0 – 2.9)	2.6 (2.2 – 3.3)	0.091
Retinol (RE), Median (IQR)	374.8 (257.6 – 762.2)	329.5 (206.4 – 803.6)	0.694
Vitamin B12 (mcg), Median (IQR)	10.0 (7.7 – 13.3)	10.1 (7.5 – 12.3)	0.920
Vitamin C (mg), Median (IQR)	156.1 (114.0 – 230.0)	170.0 (118.5 – 245.1)	0.590
Vitamin K (mcg), Median (IQR)	13.0 (11.0 – 20.7)	13.6 (11.0 – 20.8)	0.923
Calcium (mg), Median (IQR)	919.4 (766.9 – 1237.3)	932.1 (838.6 – 1284.0)	0.609
Iodine (mcg), Median (IQR)	70.7 (33.6 – 99.5)	77.1 (42.8 – 102.9)	0.577

SD- standard deviation; IQR- interquartile range; RE- retinol equivalent (1RE=1 mcg Vitamin A)

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V. CHAPTER 3

Impact of Drug Allergy on the quality of life of the patient

Study VI - “Hypersensitivity Quality of Life Questionnaire: Validation procedures and first results of the Portuguese version.”

Health Qual Life Outcomes 2021 May 10; 19 (1): 143

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Dias de Castro *et al.*
Health Qual Life Outcomes (2021) 19:143
https://doi.org/10.1186/s12955-021-01749-1

Health and Quality of Life Outcomes

RESEARCH Open Access

Drug Hypersensitivity Quality of Life Questionnaire: validation procedures and first results of the Portuguese version

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Abstract

Background: Hypersensitivity reactions to drugs are unpredictable and can be very complex and severe, even life threatening. Assess its impact on patient's health related quality of life (HRQoL) is crucial. The Drug Hypersensitivity Quality of Life Questionnaire (DrHy-Q) is the only validated disease-specific HRQoL questionnaire. We aimed to translate and cross-cultural validate the DrHy-Q to the Portuguese population. It was also our purpose to determine the impact of drug hypersensitivity on patients' HRQoL.

Methods: The translation and cross-cultural adaptation of the DrHy-Q to Portuguese was performed according to standards. Reliability of the DrHy-Q Portuguese version was assessed in terms of internal consistency and test–retest reliability. Structural validity, divergent validity (with a generic health related QoLQ-PGWBI) and discriminant validity were also evaluated. Forty patients accepted to participate in the validation phase. The Portuguese version of the DrHy-Q was applied to 260 consecutively adult patients, studied in our Department for suspected drug hypersensitivity.

Results: The Portuguese DrHy-Q showed adequate internal consistency (Cronbach's $\alpha = 0.938$), good test–retest reliability [ICC = 0.713 (95% CI 0.488–0.850] and one-dimensional structure. No significant correlation was found between the DrHy-Q and the PGWBI total scores ($r = -0.010$, $p = 0.957$). Two hundred of patients completed the study: 78.5% female; mean age = 44 ± 15 years. Mean DrHy-Q score was 36.8 ± 12.6. Two clinical factors significantly predict DrHy-Q total score: clinical manifestations and number of suspected drugs. Patients with anaphylaxis ($\beta = 11.005$; 95% CI 5.523; 16.487), urticaria/angioedema ($\beta = 7.770$; 95% CI 2.600; 12.940) and other manifestations ($\beta = 7.948$; 95% CI 1.933; 13.962) are more likely to have higher DrHy-Q total score than patients with maculopapular exanthema. Patients with ≥ 2 suspected drugs are also more likely to have worse QoL ($\beta = 7.927$; 95% CI 3.687; 12.166).

Conclusion: The Portuguese version of DrHy-Q revealed adequate validity and reliability, indicating that it is appropriate to assess the impact of drug hypersensitivity on patients' HRQoL, providing data for a better comprehension and management of our patients. Moreover, our results highlight that the severity of the drug hypersensitivity reaction and the number of suspected drugs have impact on patient's DrHy-QoL.

Background

Drug allergic reactions are adverse drug reactions mediated by immunological mechanisms. They are unpredictable and potentially severe, even life-threatening. In practice, when an immunological mechanism cannot be demonstrated, the term drug hypersensitivity is applied to adverse drug reactions that clinically resemble allergy.

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Drug hypersensitivity reactions (DHR) comprise 15% of all adverse drug reactions [1–3] and are responsible for significant morbidity and socio-economical costs [4]. Due to their unpredictable nature and potential severity, drug hypersensitivity may have an important impact on patients' health-related quality of life (HRQoL). HRQoL is a central patient reported outcome defined as those aspects of self-perceived well-being that are related to or affected by the presence of disease or treatment [5].

The assessment of HRQoL becomes critical in routine clinical practice, research and regulatory processes, namely in allergic and other chronic diseases. It allows a broader understanding of the impact on patients of their diseases and therapies [6, 7], regardless any interpretation by physician or others [8]. However, HRQoL is rarely assessed in patients with DHR probably due to the lack of specific tools for this purpose [4, 9]. The only specific tool measuring HRQoL in this field is the Drug Hypersensitivity Quality of Life Questionnaire (DrHy-Q) developed and validated by an Italian group [6]. The DrHy-Q was derived from a 34 generation-phase items to a 15-items questionnaire. The purpose was to assess the specific burden of drug hypersensitivity from the patient's perspective, specifically the impact of the drug hypersensitivity in the patient's life from emotional, physical and social point of view. This questionnaire was shown to be suitable for assessing quality of life in patients that experienced a DHR and can be used alone or in combination with other patient-reported outcome questionnaires. Subsequently, the DrHy-Q was translated and validated in some cultural settings such as Spain [9, 10], Turkey [8], Netherlands [4] and Thailand [11], but not in Portugal or in the Portuguese language.

The main aim of this study was to translate and cross-cultural validate the original Italian version of the DrHy-Q to the Portuguese population. The secondary aims were to determine the impact of drug hypersensitivity on patients' HRQoL and to compare the clinical features between patients with confirmed versus excluded drug hypersensitivity.

Methods

We used the only validated health related quality of life questionnaire in the field of drug allergy, the Drug Hypersensitivity Quality of Life Questionnaire (DrHy-Q). It is a 15-item tool, self-completed and evaluated on a five-point Likert scale [from 1 (not at all) to 5 (very much)]. Higher scores signify worse HRQoL [6].

Translation and cross-cultural adaptation of DrHy-Q

The translation and cross-cultural adaptation of this HRQoL to the Portuguese language was performed according to the standards for translation and cultural adaptation for Patient-Reported Outcomes (PROs) tools [7, 12, 13].

Forward translation

After obtaining authorization from the authors of the original instrument, the DrHy-Q [6] was translated to Portuguese language. This phase involved two local translators (Portuguese native speakers, familiar with the specific terminology and knowledgeable of the italian-speaking culture), a Portuguese HRQoL expert and a Portuguese Allergy specialist and included the following steps:

- Independently production of 2 forward versions of the questionnaire (original items, instructions and response choices), by each translator (Version 0a and Version 0b);
- Production of a single reconciled version by both translators and researchers, after discussion of the 2 forward versions (Version 1).

Backward translation

In this phase, the first reconciled forward version of the questionnaire (Version 1) was translated back into the source language by a local translator (native speaker of the target language and bilingual in source language) with no access to the original source version of the questionnaire. This backward translation, was sent to the authors in order to be compared with the original source version and detect any misunderstandings, mistranslations or inaccuracies. After the authors review and as result of this phase, a second version of the questionnaire was obtained (Version 2). Only 1 minor change was made from the first to the second version.

Pilot testing

In order to determine if the translated questionnaire is understood and the language simple and appropriate, the second version of the questionnaire was tested on a panel of 30 adult patients, through face to face interviews conducted by the same interviewer (Allergy specialist). Patients were inquired regarding any difficulty in understanding the questionnaire and their interpretation of all items was checked. This pretest phase showed that the questions were easily understandable and do not require explanation. Patients suggested only a minor change to item 2, in order to optimize the understanding. As a result of this phase, a third and final version of the translated questionnaire was produced ("Appendix").

Validation procedures

The psychometric properties of the Portuguese version of the DrHy-Q were evaluated in accordance with current guidelines [14, 15]. Data was collected using a convenience sampling method [16]. A randomized group of 40 patients accepted to participate in this validation phase.

Reliability

Reliability refers to the consistency of the measure. Internal consistency and test–retest reliability were assessed.

The test–retest reliability of the DrHy-Q was evaluated by applying the questionnaire to the randomized group of 40 patients on two different occasions, one-week apart, without any intervention, personal or clinical significant changes. Questionnaires were sent by e-mail.

Validity

Validity is the degree to which an instrument measure what is intended to measure. The validity of the DrHy-Q was assessed with 3 different analyses: structural validity, divergent validity and discriminant validity.

Structural validity was assessed with exploratory factor analysis (EFA) [17]. The PGWBI instrument was chosen for the purpose of ascertaining divergent validity. It is expected a lack of correlations between PGWBI and HRQoL since theoretically they measure different constructs. The 40 randomized patients involved in the validation phase were also asked to complete the Portuguese validated version of the Psychological General Well-being Index (PGWBI) [18]. The PGWBI is a brief self-administered questionnaire with 22 items on a six-point Likert scale. Each item is scored from 0 to 5 points, leading to a total score between 0 and 110 points, with higher values indicating better well-being [19]. The PGWBI evaluates six mood states (anxiety, depressed mood, positive well-being, self-control, general health, and vitality) and has been extensively used as an indicator of HRQoL in patients with chronic conditions [6–8]. Discriminant validity, the instrument's ability to differentiate between populations that are known or expected to differ [6], was evaluated by comparing DrHy-Q scores from patient groups with different clinical characteristics.

Drug diagnostic work-up

The drug hypersensitivity diagnostic work-up was performed according to international guidelines [1], in order to confirm or exclude the suspected drug hypersensitivity. The type and severity of reaction, the suspected drug and the availability of validated skin tests and *in-vitro tests* were considered. It included a validated questionnaire (the drug hypersensitivity questionnaire developed by European Network of Drug Allergy- ENDA) [20] and, depending on the previous referred factors, skin tests (prick, intradermal and/or patch) [21, 22], specific IgE and drug provocation test (DPT) [23].

The diagnosis of drug hypersensitivity was confirmed when skin tests were positive for validated concentrations or when specific provocation test with the suspected drug was positive. On the other hand, drug hypersensitivity diagnosis was excluded if all diagnostic procedures, including DPT with the suspected drug, were negative. Patients that did not complete the diagnostic work-up or that did not reach a conclusive diagnosis were excluded.

Study population

The final version of the translated questionnaire was applied, from July 2017 to December 2018, to 260 consecutively patients ≥ 18 years-old, studied in our Allergy Department for suspected drug hypersensitivity. The patients filled the questionnaire in their first visit to the day hospital.

Individuals that do not completed the DrHy-Q were excluded.

Social-demographic data were also collected.

Written informed consent was obtained by all individuals included in the study and the protocol was approved by the Hospital Ethics Committee (CE-66-2016).

Statistical analysis

Data were entered and analyzed using the Statistical Package for Social Sciences version 25 and statistical significance was defined as $p < 0.05$.

Variables were expressed as mean ± standard-deviation or relative and absolute frequencies. Categories with few cases were combined.

Internal consistency of the DrHy-Q was tested by Cronbach's alpha coefficient. A value of ≥ 0.70 is considered adequate for group comparison, but a value of 0.90–0.95 is needed for clinical application [24–26].

The test–retest reliability of the DrHy-Q was evaluated by applying the questionnaire to the randomized group of 40 patients on two different occasions, as described above. The 2 score sets were analyzed by the *t* test for paired samples [26]. The intra-class correlation coefficient (ICC); a two-way mixed model, was also used to assess test–retest reliability [27]. This model indicates the proportion of variance that is due to between-subject variability relative to the sum of between-subject variability and measurement error. Criteria for ICC values were < 0.4 as poor, 0.4–0.59 as fair, 0.6–0.74 as good and > 0.75 as excellent reliability.

The Bland–Altman plot was also created to visualize the agreement between the questionnaire responses at the two time points (baseline and retest) [28].

The validity of the structure was tested using the EFA [17]. In order to evaluate the number of dimensions that emerged from the data EFA with maximum likelihood was performed. To determine the number of factors to be included eigenvalues > 1 and the scree plot were examined. Items with factor loadings below 0.40 were planned to be eliminated.

To assess divergent validity, the Pearson correlation was used to analyze the correlation between the DHRQoL and the PGWBI total and the 6 domain scores. Values of −0.25 to 0 mean poor or no correlation; −0.50 to −0.25 = fair; −0.75 to −0.50 = moderate-to-good; −1.0 to −0.75 = good-to-excellent correlation.

Independent t-test or ANOVA were used to analyze differences between groups on DrHy-Q total score.

Additionally, a multiple linear regression model was designed using automatic linear modeling (ALM) [29] to evaluate which factors are associated with DrHy-Q total score. Automatic Linear Modeling is a modification and improvement of the traditional linear regression procedure, particularly in automatic variable selection and automatic data preparation [29] Multiple combinations and weighted importance are tested to determine the optimum and best-fit model possible [30]. This method also ranks predictors according to their degree of dependence from the less important to the most important.

Significant variables in the bivariate analysis were included in the model. The forward stepwise approach was used and Akaike Information Criterion Corrected (AICC) was selected as the variable entry/removal criterion. These analyses assess the discriminant validity of the DrHy-Q.

Results

Study population and Drug allergy work-up

Two hundred of patients completed the diagnostic work-up and fully filled the DrHy-Q, during the study period: 78.5% were female with a mean age of 44 ± 15 years, range [18–77]. All data in the Additional file 1.

There were more 60 patients studied during this period that were excluded: 6 patients did not fully complete the DrHy-Q; 29 did not complete the drug allergy diagnostic work-up or did not have a conclusive result and 25 patients missed the identification number in the DrHy-Q and could not be linked to the drug diagnostic work-up. These patients were not included in any analysis.

Antibiotics were the most commonly implicated drugs (168/220 patients, 84%), followed by Nonsteroidal Anti-inflammatory drugs-NSAID (44/200 patients; 22%). The main clinical presentations were maculopapular exanthema-MPE (39.5%), urticaria/angioedema (22.5%) and anaphylaxis (20%). Fifty-one percent of the reactions were immediate and 39.5% non-immediate.

After completing the drug allergy work-up 93 patients (46.5%) had the final diagnosis of confirmed drug allergy/hypersensitivity.

The likelihood of confirmed drug hypersensitivity versus a negative diagnostic work-up was significantly higher in the cases involving immediate reactions (66.3% vs 39%, $p < 0.001$), severe reactions (56.5% vs 1.5%, $p < 0.001$), anaphylaxis (40.0% vs 4%, $p < 0.001$), higher number of reactions (1.7% vs 1.3% $p < 0.001$), higher number of suspected drugs (1.5% vs 1.3% $p = 0.006$), NSAID (37.6% vs 8.4%, $p < 0.001$), general anesthetics (12.9 vs 2.8, $p = 0.008$) and an interval of time of ≤ 2 years between reaction and study (44.0% vs 25.0% $p = 0.027$).

Table 1 summarizes the socio-demographic and clinical characteristics of the patients and differences between patients with confirmed drug hypersensitivity and those with excluded drug hypersensitivity. There are some missing data mainly concerned to the socio-demographic characteristics.

Validation procedures

Thirty-one patients fully completed the questionnaires applied at the validation (83% were female with a mean age of 39 ± 12 years) (Additional file 2).

Reliability

The questionnaire's global internal consistency was 0.938, adequate not only for group comparison but also for clinical application.

No significant differences were found between test and retest ($p = 0.176$) with a mean difference of 2.5 (9.9) and a correlation of 0.722 ($p < 0.001$). The single measure of ICC was 0.713 (95% CI 0.488–0.850) indicating good test–retest reliability. The Bland–Altman plot indicate no systematic bias (Fig. 1). Only one participant fell outside the expected limits of ± 2SD (− 17.1 to 22.0).

Validity

The DrHy-Q Portuguese revealed a one-dimensional structure that explained up to 54.5% of the total variance. Table 2 provides items' factor loadings. All items had a factor loading above 0.40, therefore, none was excluded.

Concerning divergent validity, no significant correlation was found between the DrHy-Q and the PGWBI total scores ($r = -0.010$ $p = 0.957$). Only a fair and negative correlation was observed between DrHy-Q and the dimension general health of the PGWBI ($r = -0.490$; $p = 0.006$), but no correlation with the other 5 dimensions (Table 3).

Table 1 Socio-demographic and clinical characteristics of patients

	Confirmed drug hypersensitivity (N = 93)	Excluded drug hypersensitivity (N = 107)	*p* value
Gender, n (%)			
Female	74 (79.6)	83 (77.6)	0.863
Male	19 (20.4)	24 (22.4)	
Age in years, Mean (SD)	46.0 (15.0)	43.0 (15.0)	0.195
Academics studies, n (%)			
≤ 6 years	4 (11.4)	10 (24.4)	0.325
7–12	16 (45.7)	18 (43.9)	
> 12	15 (42.9)	13 (31.7)	
Atopy, n (%)			
Yes	30 (33.3)	28 (26.7)	0.347
No	60 (66.7)	77 (73.3)	
Co-morbidities, n (%)			
Yes	59 (63.4)	58 (54.7)	0.249
No	34 (36.6)	48 (45.3)	
Daily medication, n (%)			
Yes	58 (62.4)	55 (51.9)	0.153
No	35 (37.6)	51 (48.1)	
Family history of drug allergy, n (%)			
Yes	5 (5.5)	7 (6.6)	0.776
No	86 (94.5)	99 (93.4)	
Δ reaction- study, n (%)			
≤ 2 years	33 (44.0)	23 (25.0)	**0.027**
> 2 and ≤ 5 years	21 (28.0)	29 (31.5)	
> 5 years	21 (28.0)	40 (43.5)	
Type of reaction, n (%)			
Immediate	61 (66.3)	41 (39.0)	**< 0.001**
Non-Immediate	24 (26.1)	55 (52.4)	
Unknown	7 (7.6)	9 (8.6)	
Clinical manifestations, n (%)			
Anaphylaxis	36 (40.0)	4 (3.9)	**< 0.001**
Urticaria/Angioedema	24 (26.7)	21 (20.6)	
Maculopapular exanthema	25 (27.8)	54 (52.9)	
Cardiovascular symptoms	0 (0.0)	8 (7.8)	
Bronchospasm	2 (2.2)	2 (2.0)	
Gastrointestinal symptoms	0 (0.0)	3 (2.9)	
Fixed drug eruption	1 (1.1)	2 (2.0)	
Unspecified general symptoms	2 (2.2)	8 (7.8)	
Severity of reaction n (%)			
Mild	5 (21.7)	142 (72.1)	**< 0.001**
Moderate	5 (21.7)	52 (26.4)	
Severe	13 (56.5)	3 (1.5)	
Number of reactions, Mean (SD)	1.7 (1.0)	1.3 (0.5)	**< 0.001**
Number of suspected drugs, Mean (SD)	1.5 (0.8)	1.3 (0.5)	**0.006**
Suspected drug, n (%)			
ßLantibiotics	55 (59.1)	78 (72.9)	0.051
Non-ßLantibiotics	14 (15.1)	21 (19.6)	0.458
NSAID	35 (37.6)	9 (8.4)	**< 0.001**
General anesthetics	12 (12.9)	3 (2.8)	**0.008**
RCM	9 (9.7)	6 (5.6)	0.296
Corticosteroids	7 (7.5)	3 (2.8)	0.193

Table 1 (continued)

	Confirmed drug hypersensitivity (N = 93)	Excluded drug hypersensitivity (N = 107)	*p* value
Local anesthetics	1 (1.1)	7 (6.5)	0.07
PPI	5 (5.4)	2 (1.9)	0.254
Other	9 (9.8)	3 (2.8)	0.069

Bold values indicate statistical significance ($p < 0.05$)

SD, standard deviation; Δ reaction- study, interval of time between reaction and study; ßL, beta-lactam; NSAID, non- steroidal anti-inflammatory drugs; RCM, radiocontrast media; PPI, proton pomp inhibitors

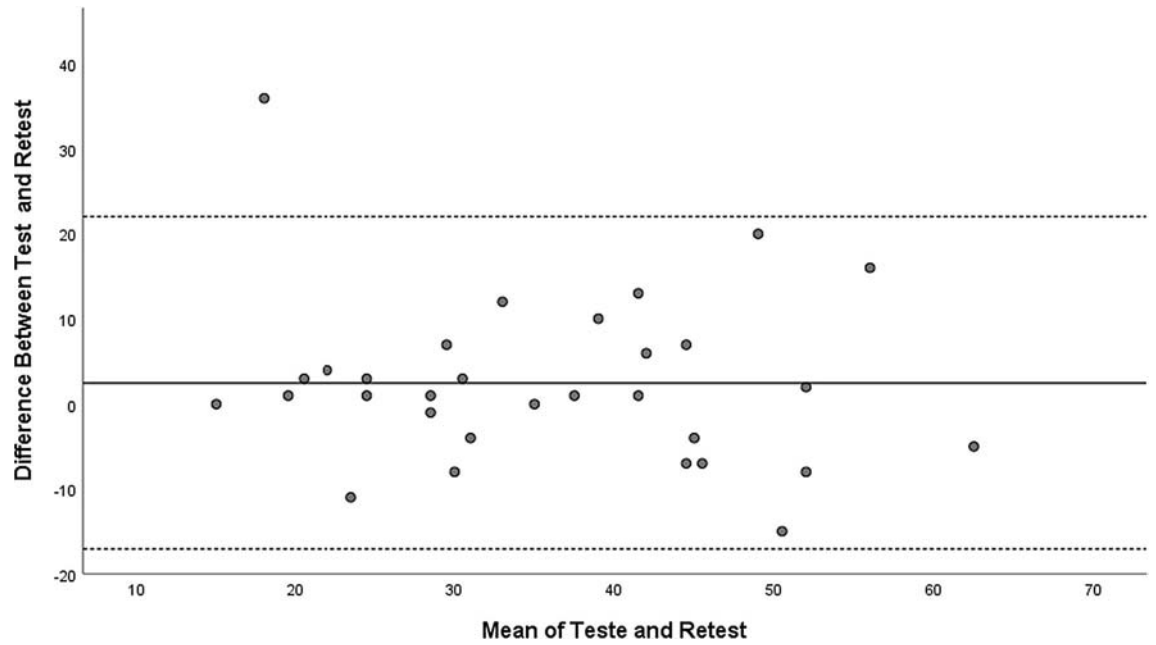

Fig. 1 The Bland–Altman plot: visualization of the questionnaire responses at the two time points (baseline and retest)

Table 2 Factor loading of each item in Portuguese version of DrHy-Q

Item	Factor loading
Since I am unable to take drugs every illness limits me more than other	0.742
I am afraid of being administered a drug during an emergency to which I am allergic	0.673
I feel frightened due to my problem of allergy reaction	0.807
The problem of adverse reaction to drugs affects my life	0.826
I would like the allergist's opinion before taking drugs prescribed by other specialists	0.666
Even a little discomfort for me is a problem	0.720
The fact that I cannot use medication safely made me feel different from others	0.735
I feel anxious due to my problem of allergy reaction	0.864
For each disease I would be confident that there is a drug that I can safely take	0.684
I am afraid I could not deal with the pain	0.558
I feel anguished due to my problem of allergy reaction	0.838
I worry every time I take a drug different from ones that cause my allergic reactions	0.812
I give up leisure activities (sport, vacations, trips) because of my problem	0.551
I'm in a bad mood due to my problem of allergy reaction	0.714
The idea of taking a medicine makes me feel anxious	0.791

Table 3 Pearson's correlation between the DrHy-Q and the PGWBI domains

PGWBI domain	r	*p*
Well being	−0.059	0.757
Anxiety	−0.300	0.107
Depression	−0.178	0.346
Self-control	−0.131	0.491
General health	−0.490	**0.006**
Vitality	−0.088	0.644
PGWBI total	−0.010	0.957

Bold value indicates statistical significance ($p < 0.05$)

DrHy-Q, Drug Hypersensitivity Quality of Life Questionnaire; PGWBI, Psychological General Well-Being Index

DrHy-Q results

In the Table 4 are represented the results of the DrHy-Q, namely the total score according to social-demographic and clinical characteristics of patients. Mean DrHy-Q score was 36.8 ± 12.6 (with median 37.0; minimum: 14.0; maximum 68.0). The following factors were found to be significantly associated with higher DrHy-Q total score or impaired quality of life: older age; presence of co-morbidities; daily medication; absence of family history of drug allergy; clinical manifestations such as anaphylaxis, urticaria/angioedema or other manifestations; severe reactions; ≥ 2 drug reactions; ≥ 2 suspected drugs and allergy to ßL-antibiotics.

Comparing DrHy-Q scores of patients with confirmed drug allergy versus excluded drug allergy we observed significant higher values in the former group (40.5 ± 12.9 vs 33.4 ± 11.2, $p < 0.001$).

Significant variables in the bivariate analysis were included in the multiple linear regression model. Two clinical factors were identified to significantly predict DrHy-Q total score: clinical manifestations and number of suspected drugs.

Patients with anaphylaxis (β = 11.005; 95% CI 5.523; 16.487), urticaria/angioedema (β = 7.770; 95% CI 2.600; 12.940) and other manifestations (β = 7.948; 95% CI 1.933; 13.962) are more likely to have higher DrHy-Q total score than patients with MPE. Patients with two or more suspected drugs are more likely to have higher DrHy-Q total score (β = 7.927; 95% CI 3.687; 12.166), as shown in Table 5. These results support the discriminant validity of the DrHy-Q.

Discussion

This study showed that the Portuguese version of DrHy-Q is a reliable and valid instrument for assessing HRQoL in patients with drug hypersensitivity.

Table 4 DrHy-Q total scores by socio-demographic and clinical characteristics of patients

	N	(%)	Mean	SD	*p* value
Gender					
Female	157	(78.1)	36.8	12.3	0.95
Male	44	(21.9)	36.9	12.7	
Age					
≤ 38 years	69	(34.3)	32.4	10.5	**0.001**
39–51	68	(31.8)	38.1	13.1	
> 51	64	(31.8)	40.2	13.0	
Academics studies					
≤ 6 years	14	(18.4)	41.9	11.5	0.058
7–12	34	(44.7)	33.2	11.7	
> 12	28	(36.8)	34.2	11.3	
Atopy					
Yes	58	(29.6)	38.9	13.2	0.120
No	138	(70.4)	35.9	12.1	
Co-morbidities					
Yes	118	(59.0)	38.5	13.3	**0.025**
No	82	(41.0)	34.4	11.3	
Daily medication					
Yes	114	(57.0)	39.1	13.0	**0.002**
No	86	(43.0)	33.7	11.4	
Family history of drug allergy					
Yes	12	(6.1)	29.8	11.1	**0.047**
No	186	(93.9)	37.2	12.6	
Δ reaction- study					
≤ 2 years	56	(33.3)	37.2	13.3	0.216
2 e 5	50	(29.8)	33.4	7.9	
> 5	62	(36.9)	36.8	14.2	
Type of reaction					
Immediate	102	(51.5)	38.3	13.5	0.132
Non-Immediate	80	(40.4)	34.6	10.9	
Unknown	16	(8.1)	38.3	14.5	
Clinical manifestations					
Anaphylaxis	79	(40.9)	41.0	13.4	**0.002**
Urticaria/Angioedema	40	(20.7)	39.2	12.5	
MPE	46	(23.8)	32.7	10.2	
Other	28	(14.5)	36.9	13.6	
Severity of reaction					
Severe	45	(23.3)	41.1	13.8	**0.008**
Moderate	58	(30.1)	36.9	12.1	
Mild	90	(46.6)	34.1	11.2	
Number of reactions					
1	127	(65.1)	34.4	12.8	**0.002**
≥ 2	68	(34.9)	40.3	11.1	
Number of suspected drugs					
1	140	(70.4)	35.2	13.0	**0.014**
≥ 2	59	(29.6)	39.9	10.4	
Class of drug					
ßL antibiotics					**0.009**
Confirmed	46	(34.6)	39.3	12.7	

Table 4 (continued)

	N	(%)	Mean	SD	*p* value
Excluded	87	(65.4)	33.5	11.8	
Non-ßL antibiotics					0.067
Confirmed	10	(28.6)	41.0	11.6	
Excluded	25	(71.4)	33.8	9.4	
NSAID					0.820
Confirmed	26	(65.0)	42.9	13.1	
Excluded	14	(35.0)	41.9	13.1	
RCM					0.324
Confirmed	7	(46.7)	33.9	12.0	
Excluded	8	(53.3)	40.4	12.5	

Bold values indicate statistical significance ($p < 0.05$)

SD, standard deviation; MPE, Maculopapular exanthema; DH, Drug hypersensitivity

Table 5 Predictive factors of DrHy-Q total score

Variable	B	*p* value	CI 95%	Importance[a]
Clinical Manifestations				0.612
Anaphylaxis	11.005	< 0.001	5.523; 16.487	
Urticaria/angioedema	7.770	0.004	2.600; 12.940	
Other manifestations	7.948	0.010	1.933; 13.962	
MPE	Ref			
Number of drugs				0.388
≥ 2	7.927	< 0.001	3.687; 12.166	
1	Ref			

MPE, maculopapular exanthema

[a] Measure of the relative importance of each predictor in estimating the model

The statistical analyses confirmed that Portuguese version of the DrHy-Q met the standards for adequate internal consistency with a Cronbach's alpha of 0.938 (Italian version 0.928) [6] along with a good test–retest reliability.

Factor analysis revealed a one-dimensional structure in line with the original Italian questionnaire[5] and other translated versions [4, 8, 11].

As expected, a negative but no significant correlation was found between the DrHy-Q and the PGWBI total scores $r = -0.010$ $p = 0.957$, since the DrHy-Q is a disease-specific questionnaire (higher scores indicating worse HRQoL) and the PGWBI is a generic quality-of-life questionnaire (higher scores indicating better well-being). Only a fair and negative correlation was observed between DrHy-Q and the dimension general health of the PGWBI ($r = -0.490$; $p = 0.006$), but no statistically significant correlation with the other 5 dimensions. These results suggest that the Portuguese DrHy-Q not only measures specific aspects of HRQoL in patients with drug hypersensitivity not assessed with generic tools, but also partially captures general aspects of HRQoL. So, these results, with slight differences with the other studies [4, 6, 8, 10, 11], corroborate an adequate divergent validity. The Italian study [6] reported negative weak correlations and other studies negative fair correlations [4, 8, 11]. A negative significant correlation for the depressed mood dimension of the PGWBI questionnaire and the Spanish DrHy-Q ($r = -0.531$; $p = 0.016$) was reported, but not with other dimensions [10].

The Portuguese DrHy-Q was able to discriminate patients according to some clinical aspects. Patients with anaphylaxis, urticaria/angioedema and other manifestations are more likely to have higher DrHy-Q total score than patients with MPE. Patients with two or more suspected drugs are also more likely to have higher DrHy-Q total score. These results are in accordance with other studies: Italian DrHy-Q also found worst HRQoL (higher scores) in patients with anaphylaxis than in patients with other milder reactions [6, 31] and the Dutch DrHy-Q was able to distinguish between patients with one and patients with more than one implicated drug [4]. The Turkish DrHy-Q could discriminate patients with ≥ 2 drug hypersensitivity reactions and patients with only one reaction, and also patients with drug-induced respiratory reactions and those without respiratory reactions [8]. The Thai DrHy-Q was able to distinguish patients with or without life-threatening severe adverse cutaneous reactions (SACRs), patients with reaction to either NSAID or ßL antibiotics, or both, and patients with one or multiple implicated drug classes [11]. Our study also showed an impaired HRQoL in patients with ≥ 2 drug hypersensitivity reactions and patients with allergy to ßL antibiotics, but this variable lost significance in multivariate model. As only 4 patients referred isolated respiratory symptoms they were included in the group of other manifestations. Patients with SCARs were not included since the severity of the reaction contraindicate the usual "in-vivo" allergy diagnostic procedures.

One of the strengths of the current study was the assessment of the potential role of socio-demographic and clinical data in the overall results DrHy-Q. We could observed how some clinical aspects of the DHR could influence the DrHy-Q scores.

Another interesting aspect of this study was the correlation between DrHy-Q scores and the final result of diagnostic work-up. Comparing DrHy-Q scores of patients with confirmed drug hypersensitivity versus excluded drug hypersensitivity we observed significant higher values in the former group. We must point out that the participants filled the questionnaire before any intervention, so they did not know any result of diagnostic work-up. These results were probably explained by the fact that some clinical variables associated with a higher

likelihood of confirmed drug hypersensitivity were also associated with higher DrHy-Q scores.

The present study only included patients studied in the day hospital for suspected drug hypersensitivity and this is one limitation, as left out patients with severe adverse cutaneous reactions (SCARs), for instances. However, these are very rare drug hypersensitivity clinical presentations, particularly in our population.

Additionally, the majority of the patients included in this study had antibiotic and/or NSAID hypersensitivity, reflecting the global prevalence of the class of drugs involved in drug hypersensitivity, but limiting the possibility of assessing the impact of hypersensitivity to other class of drugs in patients' HRQoL.

Finally, our study design did not allow us to explore the sensitivity of DrHy-Q to changes after interventions (e.g. causal diagnosis or desensitization). In future, we intend to assess the responsiveness of the DrHy-Q to interventions trough a larger and multicenter study.

Conclusions

The Portuguese version of DrHy-Q revealed adequate validity and reliability, indicating that it is appropriate to assess the impact of drug hypersensitivity on patients' HRQoL, providing data for a better comprehension and management of our patients.

Moreover, our results highlight that the severity of the drug hypersensitivity reaction and the number of suspected drugs have impact on patient's DrHy-QoL.

Appendix: Questionário

As reações alérgicas a medicamentos podem influenciar o bem-estar físico e psíquico da pessoa. Solicitamos que indique as dificuldades que tem devido a este problema

		Nenhumas	Poucas	Bastantes	Muitas	Muitíssimas
1	Como não posso tomar qualquer medicamento, qualquer doença me limita mais do que às outras pessoas	1	2	3	4	5
2	Tenho receio de que, durante uma situação urgente, me administrem um medicamento ao qual sou alérgico	1	2	3	4	5
3	Sinto-me assustado, devido ao meu problema de alergia a medicamentos	1	2	3	4	5
4	O problema de alergia a medicamentos afeta a minha vida	1	2	3	4	5
5	Gostaria de ter a opinião de um Imunoalergologista, antes de tomar um medicamento prescrito por outros especialistas	1	2	3	4	5
6	Mesmo um pequeno desconforto é um problema para mim	1	2	3	4	5
7	O fato de não poder tomar tranquilamente qualquer medicamento faz-me sentir diferente dos outros	1	2	3	4	5
8	Sinto-me ansioso, devido ao meu problema de alergia a medicamentos	1	2	3	4	5
9	Gostaria de ter a certeza de que, para cada doença, há um medicamento seguro para mim	1	2	3	4	5
10	Tenho receio de não conseguir lidar com a dor	1	2	3	4	5
11	Sinto-me angustiado, devido ao meu problema de alergia a medicamentos	1	2	3	4	5
12	Fico preocupado sempre que tomo um medicamento mesmo que seja diferente daqueles que me causaram reação alérgica	1	2	3	4	5
13	Desisti de atividades de lazer (desporto, férias, viagens) devido ao meu problema	1	2	3	4	5
14	Sinto-me com a moral em baixo, devido ao meu problema de alergia a medicamentos	1	2	3	4	5
15	A ideia de tomar um medicamento deixa-me ansioso	1	2	3	4	5

Abbreviations
DHR: Drug hypersensitivity reactions; HRQoL: Health-related quality of life; DrHy-Q: Drug Hypersensitivity Quality of Life Questionnaire; PROs: Patient-Reported Outcomes; ICC: Intra-class correlation coefficient; EFA: Exploratory factor analysis; PGWBI: Psychological General Well-being Index; ENDA: European Network of Drug Allergy; DPT: Drug provocation test; AICC: Akaike Information Criterion Corrected; NSAID: Nonsteroidal Anti-inflammatory drugs; ßL: Beta-lactam; RCM: Radiocontrast media; PPI: Proton pomp inhibitors; MPE: Maculopapular exanthema; SCARSs: Severe adverse cutaneous reactions.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12955-021-01749-1.

Additional file 1: Patient database: results of the drug hypersensitivity study and DrHy-Q.

Additional file 2: Database on the validation psychometric properties of the DrHy-Q.

Acknowledgements
Not applicable.

Authors' contributions
EDC, LR, IB and JRC designed the study; EDC, AMM and AC collected the data; EDC, JB, AMM, AC and LR did the data analysis; EDC, JB, AMM, AC and LR interpreted the data; EDC drafted the work and all authors revised it critically for important intellectual content. All authors read and approved the final manuscript.

Funding
Not applicable.

Availability of data and materials
Provided as a supplement to manuscript.

Declarations

Ethical approval and consent to participate
Written informed consent was obtained by all individuals included in the study and the protocol was approved by the Hospital Ethics Committee (CE-66-2016).

Consent for publication
All authors have approved the manuscript, agree with its submission to the journal and consent to its publication.

Competing interests
The authors declare that they have no conflicts of interest.

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Received: 26 November 2020 Accepted: 17 March 2021
Published online: 10 May 2021

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VI. GENERAL DISCUSSION

Drug therapy is often a balance between the beneficial and harmful effects of drugs and risk-benefit should always be assessed.

Given the heterogeneity, unpredictability and the potential severity of drug allergy, the management of these type of ADRs is particularly challenging. Nonetheless, exposure to a particular drug induces immune reactions in only a minority of individuals [2]. The identification of subjects at high risk is crucial and a goal of a personalized medicine [49]. It might prevent reactions to occur, allowing to adjust the drug allergy diagnostic protocols according to the patient´s risk.

It is also important to comprehend the impact of drug allergy on patient's HRQoL and the main determinant factors.

1. Clinical characteristics of DARs associated with a positive diagnostic work-up

The clinical evaluation of patients with suspected drug allergy allowing a definitive diagnosis is usually complex and a time-consuming process [2], but it is essential [2,10]. The time-consuming of these diagnostic procedures is one of the major constraints that we presently face in our clinical practice.

Knowledge regarding the clinical characteristics of DARs associated with a higher probability of a positive diagnosis could also help to support the decision to use more or less extensive diagnostic protocols. In order to address this question we assessed the clinical characteristics of DARs associated with a positive diagnostic work-up throughout this work.

In study II, the likelihood of a positive diagnostic work-up was significantly higher in children with more severe reactions and also in cases with shorter time interval between the reaction and the evaluation. This likelihood was significantly lower in children with MPE.

Multivariate analysis was not possible due to the limited number of children with confirmed ßL antibiotic allergy.

In study III, patients with drug allergy presented more severe reactions and lower number of suspected drugs, in comparison to those with excluded drug allergy. Having just one suspected drug, comparing to two or more suspected drugs and moderate-to-severe reactions, compared to mild reactions, were also predictors of drug allergy, according to the multivariate analysis.

In study IV-V, the likelihood of confirmed drug allergy versus a negative result was significantly higher in the cases involving immediate reactions, severe reactions, anaphylaxis, higher number of reactions, and a shorter interval of time between reaction and investigation. On the contrary, the likelihood of confirmed drug allergy was lower in patients with non-immediate reactions, mild reactions and MPE. In the logistic model, immediate reactions and higher number of reactions were predictors of drug allergy.

Finally, in study VI, the probability of a positive versus a negative diagnostic work-up was significantly higher in cases involving immediate reactions, severe reactions, anaphylaxis, higher number of reactions, higher number of suspected drugs and a shorter interval of time between reaction and diagnostic work-up. This probability was significantly lower in cases involving non-immediate reactions, mild reactions and MPE.

In order to measure the importance of each clinical characteristic in terms of final diagnosis of drug allergy, the following score scale was established: a predictor of drug allergy= 2 points; a positive association to drug allergy diagnosis= 1 point; no effect=0 points; a negative association= -1 point. This score scale was applied to all the studies and a final score was obtained with the sum. According to the final score, these were the clinical characteristics associated with a higher probability of a final diagnosis of drug allergy: severe reactions (with the highest score), immediate reactions, higher number of reactions and a shorter interval of time between reaction and the allergy study (the last three with an equal score). MPE was the clinical characteristic more frequently associated with a negative diagnostic work-up.

To our knowledge, this issue is not usually assessed. It was evaluated in two studies [44,97] that found similar results: a significant association with drug allergy and severe reactions [44], immediate reactions [44,97] and shorter time elapsed between reaction and evaluation [44]. Both studies involved children with suspected allergy to ßL antibiotics where there is an intense debate concerning the diagnostic protocols.

This a promising issue that should be explored with a focus on a personalized medicine in the drug allergy diagnosis.

2. Patients- related risk factors and markers of drug allergy

2.1. Demographic factors

Study II was the only one that involved a paediatric population.

The confirmatory rate of drug allergy at the end of the drug allergy diagnostic work-up for each study was as follows: 10.5% (23 in 220)- study II; 38.6% (34 in 88) -study III; 46.4% (39 in 84)- study IV-V and 46,5%(93 in 200)-study VI.

Drug allergy incidence is increasing [10] but the true incidence among children and adults remains unknown [9]. Although some studies indicate that drug allergy may account for a higher percentage of ADRs in paediatric ages comparing to adults [5], ADRs and drug allergy are expected to be considerably lower among children.

We have a higher confirmatory rate among adults in comparison to children, but no extrapolations can be made about incidence or prevalence of drug allergy.

Analysing only the studies with adults, a lower confirmatory rate was found in the study III, comparing to the other studies. This difference could be explained by the inclusion criteria. In the study III, consecutive patients were included independently of the time elapsed between the reaction and the drug allergy work-up, while in the other studies only patients with reactions in the previous 5 years were included. As previously discussed, we found that a shorter interval of time was one of the factors associated with a positive diagnostic work-up. It is known that for some drug such as ßL antibiotics, sensitivity decreases over time [98]. Moreover, important details in clinical history are dependent on patient recall that could be fail over time.

Age is not known to be an independent risk factor for drug allergy [52] and our results are in accordance. No differences were observed between patients with drug allergy and controls in any of the studies.

In terms of gender females are reported as having a higher risk for drug allergy [9,10,35,49], except in paediatric ages [9,49,55]. In this investigation, all studies involved a higher percentage of females with suspected drug allergy. However, no significant differences were found between the group of patients with confirmed vs. excluded drug allergy, except in the study II. In this study, there is a significantly higher percentage of males in the group of children with ßL allergy compared with those with a negative diagnosis.

2.2. Atopy and allergic diseases

A higher prevalence of atopy or allergic diseases in patients with drug allergy comparing to controls was not found throughout the performed studies. However, atopy was based on patient clinical history and SPT with aeroallergens were not carried out routinely in all the patients assessed, except if clinically indicated. Moreover, we did not evaluated the presence of atopy according to the DARs clinical characteristics, as severity or reaction type.

2.3. Concomitant diseases

Globally, no differences in terms of concomitant diseases were observed between patients with drug allergy and controls.

2.4. Family history of drug allergy

Family history of drug allergy was questioned in all the studies except in study III.

We found that the likelihood of ßL allergy was significantly higher in children with parental or sibling history of drug allergy in study II. To our knowledge, this is the first study showing a positive correlation between ßL allergy in children and family history of drug allergy. A recent study showed an increased risk for positive DPT to ßL in children with parental history of drug

allergy, but only in non-immediate reactions [99]. Genetic studies could add new knowledge to the field.

In immediate reactions some polymorphisms in cytokine genes have been associated with ßL allergy [34]. Another genome-wide association study in Spanish and Italian populations demonstrated a link between HLA-DRA genetic variants and penicillin allergy [100]. This study was recently extended to other populations and highlighted that HLA-DRB1*10:01 predisposes to immediate reactions to penicillins [101].

In studies IV-V and VI, a family history of drug allergy was not more common in patients than in controls. It is important to note that these studies involved a diversity of suspected drugs.

2.5. Psychological factors

In study III, patients with drug allergy revealed more psychological disturbances (higher anxiety, higher neuroticism and lower extraversion) than healthy-controls. Patients with excluded drug allergy also presented higher neuroticism levels compared to healthy-controls.

The relevance and novelty of these results come from a broad psychological evaluation that included personality type, besides anxiety, depression and alexithymia, and a diagnosis of drug allergy based in a complete diagnostic work-up. Moreover, if applied in clinical practice this type of assessment might identify patients that would benefit from psychological intervention.

2.6. Obesity, metabolic and inflammatory markers

Study IV investigated, for the first time, a potential link between drug allergy and obesity. The results highlighted that drug allergy is associated with obesity traits, assessed by different measurements. Patients with drug allergy revealed significantly higher parameters associated with both global obesity and central obesity compared with controls. They also presented higher levels of systemic inflammatory markers such as serum leptin and leptin-adiponectin ratio.

As well as the association between drug allergy and obesity, this study also showed that patients with immediate reactions to drugs revealed significantly higher obesity-related parameters compared to patients with non-immediate or unknown reactions. No significant differences were found in any of the assessed parameters with respect to the severity of the reactions or clinical manifestations.

Moreover, the logistic regression analysis revealed body fat percentage (BFP) as a predictor of drug allergy and immediate reactions to drugs. The higher the BFP, the greater the odds of developing drug allergy and an immediate reaction to drugs in particular.

In study V, the same population of patients were assessed in terms of dietary parameters and their potential association with drug allergy. Considering the advantageous aspects of a diet

pattern approach, the dietary inflammatory index (DII) was applied, for the first time, in the evaluation of patients with drug allergy. The globality of the individuals of this study, both patients and controls, revealed an anti-inflammatory DII suggestive of a Mediterranean diet pattern [61]. Although a higher DII score was found in the group of patients with drug allergy compared to the controls, this difference did not reach statistical significance.

Contrary to other studies [102-104], no significant correlations were achieved between DII scores and obesity parameters as assessed by anthropometric measurements or by bioimpedance.

Within the inflammatory and biochemical parameters assessed in these studies, the DII scores correlated with triglycerides levels in the drug allergy patients and inversely with adiponectin levels in the control group. We may speculate that these correlations only occurred in a compatible inflammatory "environment"- less anti-inflammatory in the drug allergic patients and more anti-inflammatory in the controls.

Regarding individual macro and micronutrients and other food components, no associations were found with drug allergy, except for mono-unsaturated fatty-acids (MUFAs), with a higher intake in the patient group compared to the controls. This is an unexpected result, as MUFAs have globally shown anti-inflammatory effects [105], although not accounting for the effect of whole diet and the interaction between its components.

To sum up, these studies showed for the first time, evidence of a link between obesity and drug allergy, particularly with immediate reactions. Body fat percentage emerged as a potential predictor of drug allergy.

Although patients with drug allergy revealed higher obesity and inflammatory parameters, the DII did not allow to distinguish between patients with drug allergy or controls, since both groups revealed an anti-inflammatory diet pattern.

These results are relevant and very promising as new potential markers in drug allergy were unraveled. Given that these markers are potentially modifiable through lifestyle interventions, improving obesity and systemic inflammatory parameters might thus modify drug allergy outcomes, in addition to all the global and uncountable benefits in patient´s health.

Further studies are needed to confirm the association between obesity and drug allergy. Also, to clarify the underlying immunopathologic mechanisms and the potential role of the diet in drug allergy and its outcomes.

2.7. Impact of drug allergy on patients health-related quality of life

In study VI, the translation and cross-cultural adaptation of the Drug Hypersensitivity Questionnaire (DrHy-Q) to Portuguese and the evaluation of the psychometric properties of the Portuguese version were performed in accordance with current guidelines. The Portuguese version of DrHy-Q revealed adequate validity and reliability, indicating that it is appropriate to assess the impact of drug hypersensitivity on patient´s health-related quality of life (HRQoL), providing data for a better comprehension and management of our patients. This is very relevant as a gap in the assessment of Portuguese patients with drug allergy was filled. A better and a complete approach of patients should also include PROs evaluation, since these reports come exclusively from the patient, without any involvement of interpretation by physicians or others [96]. Moreover, knowing the impact of drug allergy on patient's HRQoL could help find the best strategies able to mitigate this impact.

The Portuguese DrHy-Q was able to discriminate patients according to some clinical aspects. In this first study, the severity of the reaction and the number of suspected drugs had a significant impact on patient's DrHy-QoL. More severe reactions and a greater number of suspected drugs were predictors of worse HRQoL. These interesting results are in agreement with other studies [9,106,107]. Severe reactions are expected to be a more intense experience and a greater number of suspected drugs may be more limiting for the patient. Both factors would have an important impact on patient´s HRQoL.

2.8. A broad evaluation of the patient with drug allergy

The globality of the studies performed throughout this investigation brought about a broad assessment of patients with drug allergy, besides the clinical aspects of drug allergy. This is relevant and in accordance with a whole vision of the patient, as each and all parts will be closely linked.

3. Limitations of the studies

All the studies performed have a similar design: are observational, cross-sectional and case-control studies. All are prospective studies except study II.

The primary outcome of study II was to characterize the confirmed cases of allergy to ßL antibiotics in children, investigating potential risk-factors. Given the low confirmatory rate in previous published studies [44, 98, 99, 108], we decided to carry out a retrospective study, since a prospective study in a limited period of time would not allow for a significant sample size to answer to the main objective of the study. So, a retrospective review of the clinical data from all children assessed in our Allergy and Clinical Immunology Department for suspected ßL allergy

over a six-year period was performed. Even so, the low number of children with confirmed diagnosis did not allow to perform a multivariate analysis. Also, genetic studies were not performed in our study, as would be desirable.

Retrospective studies depend on review of data previously obtained and that were not designed for the purpose of the study, with high probability of missing data. However, this issue was not a problem in this study.

Retrospective studies usually have more potential sources of bias than prospective studies, such as selection bias because controls are often recruited by convenience sampling. In all the studies involved in this research, we performed an adaptive randomization, according to the results. This a relevant point. The selection of patients and controls was made according to several reasons. First, consecutive patients that met the inclusion criteria were invited to participate, preventing selection bias. Second, all the studies were randomized, reducing the likelihood that the group of patients and controls differ substantially and minimizing potential confounders. Third, the randomization was done according to the result of the drug allergy diagnostic work-up. Moreover, this result was only known at the end of the study. Fourth, the selection of patients and controls that are going to be studied in clinical practice, and not selected from a database (e.g. CPARA-Portuguese catalog of allergies and other adverse reactions) prevents misdiagnosis. Fifth, the selection of patients and controls that are going to be studied in clinical practice, allowed to investigate clinical characteristics of DARs associated with a positive diagnostic work-up. In case we have used other controls with no suspected DAR, this global objective of this investigation could not be pursued. Finally, selecting patients and controls who are studied in routine clinical practice, as usual and avoiding intentional visits to the hospital exclusively for the study is crucial. Minimizing the inconvenience to the patients, improves recruitments and reduces dropouts.

On the other hand, with these selection criteria, the studies performed did not include all the types/subtypes of immune reactions to drugs mainly because some of them are rare. In addition, life-threatening SCARs are extremely severe and the usual *in-vivo* allergy diagnostic procedures are contra-indicated.

In study III, the sample for the analysis included patients with drug allergy, patients with excluded drug allergy and also a control group of healthy volunteers. This last group was included since it would be expected that patients with excluded drug allergy also presented psychological disturbances. The control group was randomly recruited and it was mainly composed by the individuals who accompanied the patient to the hospital, but also included nonmedical faculty staff. This could be considered a limitation.

In terms of the objectives of each study, they are specific, measurable and clinically relevant. Furthermore, they are approachable and feasible and also mostly innovative.

The sample size was adequate to the primary aim defined in all studies, excepted in study V**.** In this study, the sample size could be a limitation. Not only because of the results, not necessary dependent on this fact. An analysis according to the standardized terciles or quartiles, usually used in other studies was not possible. The global anti-inflammatory diet pattern of our sample might also be responsible, as none of the patients were in the highest anti-inflammatory tercile or quartile. There are no studies involving patients with drug allergy, but studies that applied the DII to other populations used larger samples. However, the sample size in this case was defined based on the main objective of the study IV and the population assessed in both studies was the same.

In study III and VI, it was not possible to perform analysis by subgroups. It would have been interesting. However, it should not be considered a limitation as it was not the main purpose of these studies.

The sample sizes in prospective studies involving patients with drug allergy are usually moderate and 2 main reasons may explain this constraint: one is that drug allergy is not frequently confirmed after a diagnostic work-up, and another is that diagnostic procedures take a significant time until final diagnosis.

Statistical analysis of data and more specific issues concerning each study, such as patient assessment and respective used tools for that purpose were previously discussed and were globally appropriate.

Finally, the cross-sectional study design of the studies did not allow to establish any causal association.

4. Future perspectives

Under the umbrella of drug allergy there is a great heterogeneity of clinical manifestations and immunological mechanisms [2]. Given this heterogeneity, it is difficult to establish links with other allergic diseases. Research on risk factors for drug allergy, including this present investigation, revealed that atopic patients or patients with allergic diseases are not known to be at increased risk [9,44,49,56]. Although, if we focus on Type I DARs, it is possible that different results will emerge. In fact, it has been reported that allergic diseases may predispose to more severe IgE-mediated DARs [57]. A recent study involving adult patients with immediate DARs to ßL antibiotics found that several parameters of atopy were predictors of this type of reactions [58]. Moreover, in this work we found an association between drug allergy and obesity, particularly in immediate reactions and the possibility of this association being based on a Type

I immune mechanism is discussed. These are very interesting and very promising findings. In near future, we intend to continue this investigation, probably with Type I reactions as a particular target. The potential role of the diet will also be further investigated.

Exploring the genetic factors in our patients with ßL allergy will be another objective.

Finally, we intend to maximize the potential benefits of the new tool, the DrHy-Q Portuguese version, in our clinical practice. The next step will be a large and multicenter study in order to assess the responsiveness of the DrHy-Q to interventions.

VII. CONCLUSIONS

Exposure to a particular drug induces immune reactions only in a minority of individuals. Although, these reactions are usually unpredictable and potentially severe. Identifying subjects at higher risk is crucial in order to prevent reactions to occur and also adjust the drug allergy diagnostic protocols according to the patient´s risk. It is also important to comprehend the impact of drug allergy on patient's HRQoL and the main determinant factors.

Major findings of this thesis are summarized as follows:

- There is evidence, for the first time, of a link between obesity and drug allergy, particularly with immediate reactions:
    - Patients with drug allergy revealed significantly higher parameters associated with both global obesity and central obesity, compared to controls.
    - Patients with drug allergy also presented higher levels of systemic inflammatory markers such as serum leptin and leptin-adiponectin ratio.
    - Patients with immediate DARs revealed significantly higher obesity-related parameters and systemic inflammatory markers.
    - BFP emerged as a predictor of drug allergy and of immediate reactions to drugs. The higher the BFP, the greater the odds of developing drug allergy and particularly an immediate reaction.
- Although patients with drug allergy revealed higher obesity and systemic inflammatory parameters, the DII did not allow to distinguish between patients with drug allergy or controls:
    - Patients with drug allergy revealed a less anti-inflammatory diet assessed by DII compared to controls, but this difference did not reach statistical significance.
    - The DII scores correlated with triglycerides levels in the drug allergic patients group and inversely with adiponectin levels in the control group.
- Patients with drug allergy revealed a specific psychological profile:
    - These patients presented more psychological disturbances (higher anxiety, higher neuroticism and lower extraversion) than healthy-controls.
- Genetic factors could be important in ßL allergy:
    - The likelihood of ßL allergy was significantly higher in children with family history of drug allergy.
- The Portuguese version of DrHy-Q demonstrated adequate validity and reliability, revealing ability to discriminate patients according to clinical aspects:
    - More severe reactions and a greater number of suspected drugs were predictors of worse HRQoL.

- The probability of a positive drug allergy diagnostic work-up was associated with some clinical aspects of DARs:
    - Severe reactions, immediate reactions, higher number of reactions and a shorter interval of time between reaction and study were associated with a higher likelihood of confirmed drug allergy.
    - On the opposite, MPE was associated with a higher probability of a negative diagnostic work-up.

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