

Original Article



Psychological profiles of patients with suspected drug allergy

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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

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.

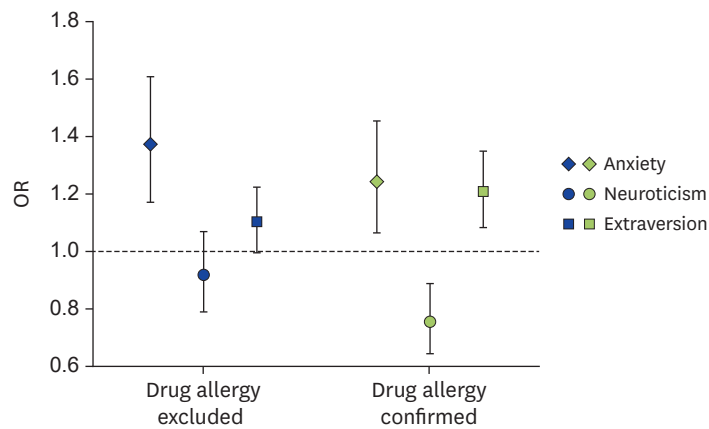


Fig. 1. Predictors of drug allergy status. OR: odds ratio for psychological features from multinomial logistic regression analysis predicting drug allergy (control group is the reference category) adjusted for neuroticism, extraversion, and anxiety. Error bars: 95% confidence interval.

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		
Yes	1 (3.0)	3 (8.8)
No	32 (97.0)	31 (91.2)
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.

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 administered) ($p = 0.016$).

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)	<i>p</i> 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.

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.

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REFERENCES

1. Michel FB. Psychology of the allergic patients. *Allergy* 1994;49:28-30.
[PUBMED](#) | [CROSSREF](#)
2. Kovács M, Stauder A, Szedmák S. Severity of allergic complaints: the importance of depressed mood. *J Psychosom Res* 2003;54:549-57.
[PUBMED](#) | [CROSSREF](#)
3. Hashizume H, Takigawa M. Anxiety in allergy and atopic dermatitis. *Curr Opin Allergy Clin Immunol* 2006;6:335-9.
[PUBMED](#) | [CROSSREF](#)
4. Buske-Kirschbaum A, Ebrecht M, Gierens A, Hellhammer DH. Personality characteristics in chronic and non-chronic allergic conditions. *Brain Behav Immun* 2008;22:762-8.
[PUBMED](#) | [CROSSREF](#)
5. Patten SB, Williams JV, Lavorato DH, Eliasziw M. Allergies and major depression: a longitudinal community study. *Biopsychosoc Med* 2009;3:3.
[PUBMED](#) | [CROSSREF](#)
6. Mehrinejad SA, Jalili M, Ghaffari J. Comparison between psychological traits of patients with various atopic allergic diseases and healthy volunteers: a case-control study. *Indian J Allergy Asthma Immunol* 2013;27:42-6.
[CROSSREF](#)
7. Yii AC, Koh MS. A review of psychological dysfunction in asthma: affective, behavioral and cognitive factors. *J Asthma* 2013;50:915-21.
[PUBMED](#) | [CROSSREF](#)
8. Baiardini I, Sicuro F, Balbi F, Canonica W, Braido F. Psychological aspects in asthma: do psychological factors affect asthma management? *Asthma Res Pract* 2015;1:7.
[PUBMED](#) | [CROSSREF](#)
9. Kim DH, Han K, Kim SW. Relationship between allergic rhinitis and mental health in the general Korean adult population. *Allergy Asthma Immunol Res* 2016;8:49-54.
[PUBMED](#) | [CROSSREF](#)
10. Zhang L, Zhang X, Zheng J, Wang L, Zhang HP, Wang L, Wang G. Co-morbid psychological dysfunction is associated with a higher risk of asthma exacerbations: a systematic review and meta-analysis. *J Thorac Dis* 2016;8:1257-68.
[PUBMED](#) | [CROSSREF](#)
11. Muñoz-Cano R, Ribó P, Araujo G, Giralt E, Sanchez-Lopez J, Valero A. Severity of allergic rhinitis impacts sleep and anxiety: results from a large Spain cohort. *Clin Transl Allergy* 2018;8:23.
[PUBMED](#) | [CROSSREF](#)
12. Sastre J, Crespo A, Fernandez-Sanchez A, Rial M, Plaza V; investigators of the CONCORD Study Group. Anxiety, depression, and asthma control: changes after standardized treatment. *J Allergy Clin Immunol Pract* 2018;6:1953-9.
[PUBMED](#) | [CROSSREF](#)
13. Retamales R. Enfermedades alérgicas e transtornos psiquiátricos. *Actas Luso Esp Neurol Psiquiatr* 1994;22:284-9.
14. Zung W. A rating instrument for anxiety disorders. *Psychosomatics* 1971;12:371-9.
[PUBMED](#) | [CROSSREF](#)
15. Andrade LH, Gorenstein C. Aspectos gerais das escalas de avaliação de ansiedade. *Rev Psiquiatr Clin (Santiago)* 1998;6:285-90.
16. Zung WW. The measurement of affects: depression and anxiety. *Mod Probl Pharmacopsychiatry* 1974;7:170-88.
[PUBMED](#) | [CROSSREF](#)
17. Zung W. A self-rating depression scale. *Arch Gen Psychiatry* 1965;12:63-70.
[PUBMED](#) | [CROSSREF](#)
18. Veríssimo R. Versão Portuguesa da Escala de Alexitimia de Toronto de 20-itens--I. *Acta Med Port* 2001;14:529-36.
[PUBMED](#)
19. Rief W, Heuser J, Fichter M. What does the Toronto Alexithymia Scale TAS-R measure? *J Clin Psychol* 1996;52:423-9.
[PUBMED](#) | [CROSSREF](#)

20. Swift L, Stephenson R, Royce J. The 20-item Toronto Alexithymia Scale: validation of factor solutions using confirmatory factor analysis on physiotherapy out-patients. *Psychol Psychother* 2006;79(Pt 1):83-8.
[PUBMED](#) | [CROSSREF](#)
21. Säkkinen P, Kaltiala-Heino R, Ranta K, Haataja R, Joukamaa M. Psychometric properties of the 20-item toronto alexithymia scale and prevalence of alexithymia in a finnish adolescent population. *Psychosomatics* 2007;48:154-61.
[PUBMED](#) | [CROSSREF](#)
22. Serra AV, Ponciano E, Freitas FJ. Resultados da aplicação do Eysenck Personality Inventory a uma amostra de População Portuguesa. *Psiquiatria Clínica* 1980;1:127-32.
23. Demoly P, Adkinson N, Brockow K, Castells M, Chiriac AM, Greenberger PA, Khan DA, Lang DM, Park HS, Pichler W, Sanchez-Borges M, Shiohara T, Thong BYH. International Consensus on drug allergy. *Allergy* 2014;69:420-37.
[PUBMED](#) | [CROSSREF](#)
24. Demoly P, Kropf R, Bircher A, Pichler WJ. Drug hypersensitivity questionnaire (ENDA-EAACI). *Allergy* 1999;54:999-1003.
[PUBMED](#) | [CROSSREF](#)
25. Brockow K, Romano A, Blanca M, Ring J, Pichler W, Demoly P. General considerations for skin test procedures in the diagnosis of drug hypersensitivity. *Allergy* 2002;57:45-51.
[PUBMED](#)
26. Brockow K, Garvey LH, Aberer W, Atanaskovic-Markovic M, Barbaud A, Bilo MB, Bircher A, Blanca M, Bonadonna B, Campi P, Castro E, Cernadas JR, Chiriac AM, Demoly P, Grosber M, Gooi J, Lombardo C, Mertes PM, Mosbech H, Nasser S, Pagani M, Ring J, Romano A, Scherer K, Schnyder B, Testi S, Torres M, Trautmann A, Terreehorst I; ENDA/EAAACI Drug Allergy Interest Group. Skin test concentrations for systemically administered drugs -- an ENDA/EAAACI Drug Allergy Interest Group position paper. *Allergy* 2013;68:702-12.
[PUBMED](#) | [CROSSREF](#)
27. Aberer W, Bircher A, Romano A, Blanca M, Campi P, Fernandez J, Brockow K, Pichler WJ, Demoly P. Drug provocation testing in the diagnosis of drug hypersensitivity reactions: general considerations. *Allergy* 2003;58:854-63.
[PUBMED](#) | [CROSSREF](#)
28. Hosmer DW, Lemeshow S. *Applied logistic regression*. 2nd ed. New York: John Wiley & Sons; 2000.
29. Hermes B, Hein UR, Henz BM. Assessment of psychological aspects during systemic provocation tests in patients with pseudoallergic drug reactions. *J Eur Acad Dermatol Venereol* 2006;20:800-3.
[PUBMED](#) | [CROSSREF](#)
30. Soyüğüit Ş, Aydın Ö, Yılmaz İ, Özdemir SK, Cankorur VS, Atbaşoğlu C, Çelik GE. Evaluation of drug provocation test-related anxiety in patients with drug hypersensitivity. *Ann Allergy Asthma Immunol* 2016;117:280-4.
[PUBMED](#) | [CROSSREF](#)
31. Losappio LM, Cappai A, Arcolaci A, Badiu I, Bonadonna P, Boni E, Bussolino C, Caminati M, Galati P, Heffler E, Intravaia R, Mauro M, Massaro I, Romano A, Rumi G, Parolo A, Pizzimenti S, Nichelatti M, Pastorello EA, Nichelatti, Pastorello EA. Anxiety and depression effects during drug provocation test. *J Allergy Clin Immunol Pract* 2018;6:1637-41.
[PUBMED](#) | [CROSSREF](#)
32. Sansone RA, Gentile J, Markert RJ. Drug allergies among patients with borderline personality symptomatology. *Gen Hosp Psychiatry* 2000;22:289-90.
[PUBMED](#) | [CROSSREF](#)
33. Macy E, Ho NJ. Multiple drug intolerance syndrome: prevalence, clinical characteristics, and management. *Ann Allergy Asthma Immunol* 2012;108:88-93.
[PUBMED](#) | [CROSSREF](#)
34. Omer HM, Hodson J, Thomas SK, Coleman JJ. Multiple drug intolerance syndrome: a large-scale retrospective study. *Drug Saf* 2014;37:1037-45.
[PUBMED](#) | [CROSSREF](#)
35. Blumenthal KG, Li Y, Acker WW, Chang Y, Banerji A, Ghaznavi S, Camargo CA, Zhou L. Multiple drug intolerance syndrome: epidemiology and association with anxiety and depression. *Allergy* 2018;73:2012-23.
[PUBMED](#) | [CROSSREF](#)
36. Ong D, Popat A, Knowles SR, Arrowood JS, Shear NH, Binkley KE. Objective psychological measurement and clinical assessment of anxiety in adverse drug reactions. *Can J Clin Pharmacol* 2004;11:e8-16.
[PUBMED](#)

37. Berrino A, Voltolini S, Bignardi D, Fasce C, Minale P, Macchi M, Troise C. Psychological aspects of drug intolerance. *Eur Ann Allergy Clin Immunol* 2005;37:90-5.
[PUBMED](#)
38. Hassel JC, Danner D, Hassel AJ. Psychosomatic or allergic symptoms? High levels for somatization in patients with drug intolerance. *J Dermatol* 2011;38:959-65.
[PUBMED](#) | [CROSSREF](#)
39. De Pasquale T, Nucera E, Boccascino R, Romeo P, Biagini G, Buonomo A, Colagiovanni A, Pecora V, Aruanno A, Rizzi A, Lombardo C, Sabato V, Gasbarrini GB, Patriarca G, Schiavino D. Allergy and psychological evaluations of patients with multiple drug intolerance syndrome. *Intern Emerg Med* 2012;7:41-7.
[PUBMED](#) | [CROSSREF](#)
40. Patriarca G, Schiavino D, Nucera E, Colamonico P, Montesarchio G, Saraceni C. Multiple drug intolerance: allergological and psychological findings. *J Investig Allergol Clin Immunol* 1991;1:138-44.
[PUBMED](#)
41. Comert S, Erdogan T, Demir AU, Karakaya G, Kalyoncu AF. Evaluation of anxiety levels and factors associated with positive test results in patients with drug hypersensitivity. *Allergy Asthma Proc* 2015;36:439-46.
[PUBMED](#) | [CROSSREF](#)
42. Baiardini I, Gaeta F, Molinengo G, Braido F, Canonica W, Romano A. Quality-of-life issues in survivors to anaphylactic reactions to drugs. *Allergy* 2015;70:877-9.
[PUBMED](#) | [CROSSREF](#)
43. Blanca M, Romano A, Torres MJ, Fernández J, Mayorga C, Rodriguez J, Demoly P, Bousquet PJ, Merk HF, Sanz ML, Ott H, Atanasković-Marković M. Update on the evaluation of hypersensitivity reactions to betalactams. *Allergy* 2009;64:183-93.
[PUBMED](#) | [CROSSREF](#)