

PSYCHOLOGICAL ASPECTS OF DRUG INTOLERANCE

A.-M. Berrino (1), S. Voltolini (2), D. Bignardi (2),
C. Fasce (1), P. Minale (2), M. Macchi (1), C. Troise (2)

SUMMARY: A consecutive unselected series of 50 patients suffering from drug intolerance was evaluated by allergological and psychological tests. We wanted to verify the existence of a correlation between some psychological characteristics (hysteria, depression and Ego Integrity), and some clinical aspects (number and type of episodes, severity and probability of the reactions). We confirmed the prevalence of female sex in these disorders, particularly in middle-aged married women. The mean score of hysteria in the whole sample was lightly higher than normal. Moreover a relevant number of subjects (24%) scored higher than the cut off for clinical depression, with a significant difference in comparison to the overall prevalence of depression in the general population. Finally, the analysis of clinical variables considered in our patients showed that subjects with a history of less serious reactions and unlikely reactions scored higher in depression and hysteria scales. The importance of psychological evaluation of drug intolerance patients is discussed and confirmed.

Key-words: Drug intolerance - Personality - Hysteria - Depression.

INTRODUCTION

In the daily clinical practice of the allergist it is clear that the allergic or intolerant patient often shows some emotional needs or a different degree of psychological distress. Although psychological factors have long been associated with allergic diseases, mostly with respiratory and cutaneous symptoms, only a few reports in the medical literature have focused this topic in drug intolerant patients. In an extensive French study (1) on 1833 allergic subjects (asthma, rhinitis and cutaneous allergy) three psychological patterns emerged. The Authors refused the often-stated theory of a unique psychological profile in allergic patients and conclude that psychological factors may be strictly connected to the biologic allergic sensitivity. Patriarca (2) studied a particular subgroup of patients, affected by "multiple drug intolerance", evaluated by a psychodiagnostic test (Rorschach's test). A negative psychological constitution, with a little ability to express emotions and a large expression of depressive feelings was demonstrated in this kind of patients. Retamales (3) found that patients allergic to drugs presented a higher number of psychological disorders compared to the allergic rhinitis and asthma patients.

The psychogenic aspects of adverse reactions to specific drugs have been taken into consideration only for local anesthetics. In fact, in this case the most likely causes of reactions are considered from some AA to be psychogenic (4), sometimes as a manifestation of anxiety to the act of receiving an injection (5); however, in the clinical practice, fear responses are frequently unrecognised, while allergic reactions are over reported.

With the aim to improve our diagnostic and therapeutic procedure in case of adverse drug reactions, we started an interdisciplinary approach by a combination of psychological and allergological evaluation. Preliminary data of this study suggested that drug intolerance patients scored high in some scales of the MMPI (6), such as Hysteria, Hypochondria and Depression.

For this reason, we decided to develop a specific study in order to further elucidate psychological aspects of drugs intolerant patients. In particular, we were interested in the correlation between clinical and psychological data. Firstly, we wanted to confirm the observation that emotional and psychological disturbances are frequent in drug intolerance patients. Secondly, we wanted to verify the existence of a correlation between some specific psychological characteristics and some clinical aspects of drug reactions. In particular, we made the hypothesis that subjects with a history of multiple drug intolerance, which often have episodes of low clinical severity, could

(1) Psychiatric Unit, ASL n° 3 Genoa (Italy).

(2) Allergy Unit, San Martino Hospital, Genoa (Italy).

score highest in hysteria and depression scales. Finally, we wanted to verify in these patients the frequency of reactions to the placebo administration.

MATERIALS AND METHODS

Subjects

All consecutive admissions for drug intolerance to the Allergy Unit of San Martino Hospital, Genoa, during a period of seven months were considered. We excluded patients with reactions to local anaesthetics, because they are submitted to a different diagnostic protocol, in comparison to other drugs. Fifty patients, 37 (74%) women and 13 (26%) men, were included (table 1). Age ranges uniformly from 18 to 61 years, with a mean age of 39 years. 28 subjects (56%) are married. The majority has secondary school education, 17 patients have primary school education and 5 are graduated. More than half of them are employed (72%), the others (28%) are unemployed, retired or housewives.

DEMOGRAPHIC DATA	N° PATIENTS	%
Sex		
Male	13	26
Female	37	74
Marital status		
Single	17	34
Married	28	56
Divorced, Widowed	5	10
Education		
Primary (low) school	2	4
Primary (middle) school	15	30
Secondary (high) school	28	56
University Degree	5	10
Employment		
Employee	36	72
Unemployed, Retired, Housewives	14	28
Total subjects	50	100

Table 1: Demographic data in the sample (n=50).

Psychological evaluation

During the allergist consultation it was proposed to all drug intolerant patients to participate voluntarily to the research, filling out a brief demographic form and

two psychological questionnaires. All the questionnaires were delivered by a psychologist after a brief explication of the research objectives. Informed consensus was obtained.

Two scales of the MMPI reduced version, the Hysteria Scale (HY) and the K-Scale, and a Self Rating Test of Depression were selected for the evaluation. *The Hysteria Scale* was selected because of positive results of our previous explorative study and because of the evidences present in the literature (7). This scale evaluates hysteric traits of personality by items concerning somatic problems and in particular the ones related to fears, distress and nervous tension. *The K-Scale* was selected for two reasons: to detect the degree of sincerity of subjects and to evaluate Ego integrity. K-Scale is one of the three reliability scales of MMPI. Finally we chose *The Zung Depression Inventory*, a short self rating questionnaire frequently used in research studies, for the evaluation of depressive mood. It is composed by 20 items that explore affective, somatic and psychological aspects of depression on a four levels Likert scale (8).

Clinical Evaluation

■ Was performed by:

➤ **Clinical history** to document any previous drug reaction. When conducted with accuracy, by using some particular clinical criteria (e.g. time relation, previous episodes, clinical outcome and therapies, reappearance with reintroduction) it allows the allergist to get to a first judgment about severity and probability of a cause-effect relation of the reactions. At the end of the evaluation the severity of the episodes was graded on a 3 level scale (low, moderate, high). The probability that each reaction was attributable to the suspected drug was classified as "likely", "possible" or "unlikely" (9, 10).

➤ **Laboratory and /or skin tests:** performed not in every cases, but when they are reliable and appropriate, depending on the drug involved, type and severity of previous reactions.

➤ **Oral challenge test:** usually performed with an alternative drug, except in some cases in which the suspected drug was the best available for a clinical use and the previous reaction was benign. The challenge is done under controlled conditions in a single blind way, by giving orally in a first day four doses of a placebo (water or an empty capsule), one every 30 minutes. During a second day, an incrementing dose of the real drug is given every 30 minutes, getting to a daily therapeutic dose of the drug. If any symptom or sign appear a careful medical examination suggests to stop the test or to continue in the administration, sometimes with an intermittent single placebo dose.

Results of Clinical Evaluation

As we can see in table 2, 56% of patients gave a history of reactions to a single drug category, 44% to several different drugs. The majority of males (69%) had an intolerance to a single kind of drug ("monovalent"), while no differences were observed in the female subjects (48% monovalent, 52% polyvalent). Drugs involved were: antibiotics in 37 patients (74%), NSAID in 25 patients (50%), different drugs only in 3 cases (6%). 13 patients (26%) accused contemporary antibiotics and NSAID of untoward reactions.

Three quarters (75%) of the subjects reported more than one drug intolerance episodes, but the severity was high only in 4% and "moderate" in 67% (figure 1). Urticaria-angioedema (65%) was the most frequent among the possible reactions (cutaneous rush, exfoliating dermatitis, asthma, fever and various different complains).

About the probability of the reactions, half of them were judged as likely, 23% possible and 25% improbable (figure 2).

Two patients were not submitted to the oral challenge test. Nine out of 48 (19%) who were challenged showed some reactions to the placebo administration: only two among them were males. The reactions to the placebo were: cutaneous rush, gastrointestinal reactions, headache, dyspnoea, itching, sleepiness, paresthesias.

Statistical analysis

Statistical analysis was performed with *SPSS 10.0*. Three orders of variables: socioeconomics, allergological and psychological were considered. All the psychological variables are quantitative, while all the allergological ones are qualitative. The allergological

	N° patients	%		N° Patients	%
Intolerance			Clinical reactions		
Monovalent	27	56	Rush	7	15
Polyvalent	21	44	Urticaria- angioedema	31	65
Episodes			Asthma	2	4
Single	12	25	Exfoliating dermatitis	2	4
Two or more	36	75	Fever	1	2
Reaction to placebo			Others	5	10
Yes	9	19			
No	39	81			
Total subjects	48	100	Total subjects	48	100

Table 2: Clinical evaluations in the sample (n=48).

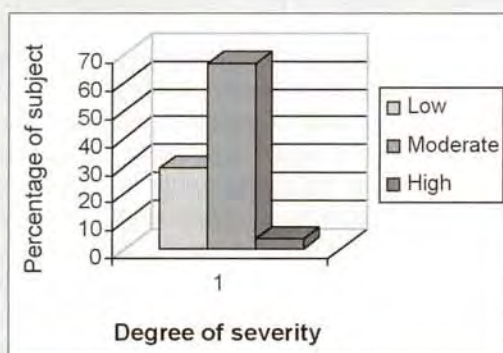


Figure 1: Severity of allergic reactions.

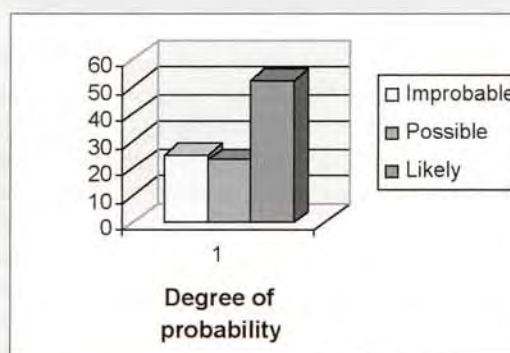


Figure 2: Probability of allergic reactions.

variables analyzed are: intolerance type, number of episodes, type of reactions to drugs, reaction to placebo during the challenge test, severity and probability of the adverse drug reactions. Psychological variables analysed are: Ego integrity and reliability, hysteria, depression. The statistical significance of the difference among groups was evaluated with t student.

We decided to consider together moderate and high severity in comparison to low severity reactions; in the same way, we did for possible and likely in comparison to improbable reactions.

RESULTS

All the psychological variables show a normal distribution in the group (figure 3, 4, 5). As we can see in table 3, the mean score of the sample in the K-Scale (m. 13.5, d.s. 4.47) transformed in T scores (T=52) is normal. Subjects were sincere and their abilities to evaluate themselves were conserved. The mean score on Hysteria Scale (HY) (m. 24.96, d.s. 6.17) transformed in T scores (T=61) is lightly higher than normal. The mean score in the Zung Test (m. 35.03,

d.s. 7.12) transformed in normal scores (Z=44) does not show depressive mood in the whole sample. Nor ever, as this variable is normally distributed, 15 patients (24%) scored higher than the cut off (Z=50) for clinical depression (figure 5)

No significant sex differences emerged from psychological evaluation. We noticed that subjects with high education (secondary school or university degree) have a higher score in the K-Scale ($t=2.9$; $p<0.01$) than subjects with low education, as is known in literature (11). This means that highly education subjects have a more defensive approach to test.

As we can see in table 4, there is a weak negative correlation between the K-Scale and the Depression Scale ($r=-0.358$). Subjects scoring high in the K-Scale, that means a good Ego Integrity, obtained low scores in the Depression Scale and vice versa. This result may be explicated by defensive mechanisms, which can control patient's emotions not allowing the manifestation of depressive symptoms. A weak positive correlation was also found between the two scales HY and K of MMPI ($r=0.337$), in agreement with the results of other Authors (11).

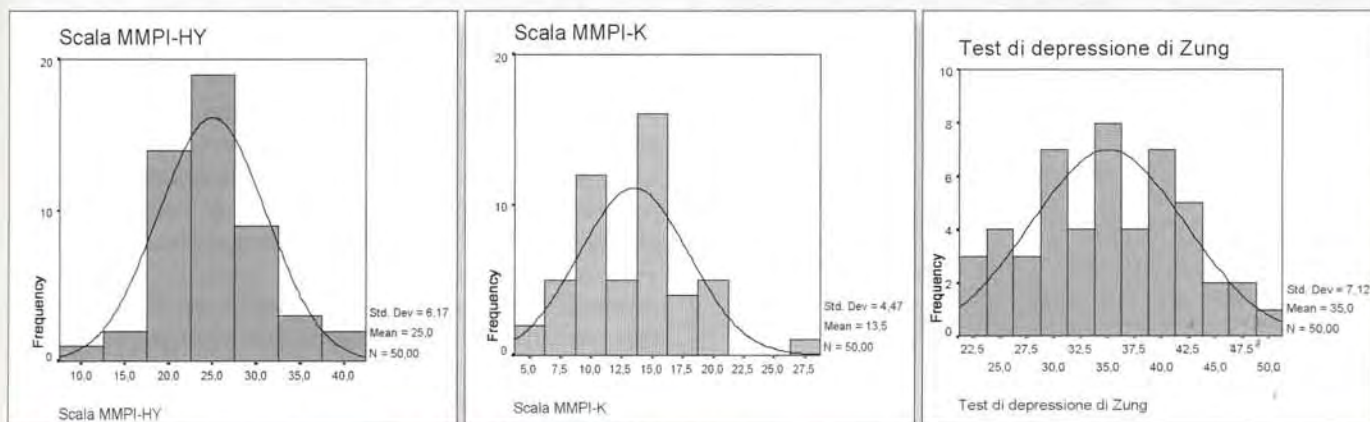


Figure 3, 4, 5: Distribution of scores of the three psychological variables.

	N	Mean	Std. deviation	Minimum	Maximum
MMPI-HY Scale	50	24,96	6,17	10	42
MMPI-K Scale	50	13,50	4,47	4	27
Depression Inventory of Zung	50	35,03	7,12	22	51

Table 3: Descriptive Statistics of psychological variables.

	MMPI-HY Scale	MMPI-K Scale
MMPI-HY Scale		
Pearson Coef.		
p Sig. (2 code)		
MMPI-K Scale		
Pearson Coef.	0.337*	
p Sig. (2 code)	0.017	
Zung Test		
Pearson Coef.	0.237	-0.358*
p Sig. (2 code)	0.098	0.011

Table 4: Correlations among different psychological variables.

* Significance $p<0.05$ (2 code).

If we analyse the relation between psychological and clinical variables, we do not find any significant correlation between high scores in the HY Scale or Depression Scale and positive reaction to placebo. Also the clinical variables as intolerance type, reaction type and number of episodes do not correlate to the considered psychological parameters. A significant result was the presence of higher scores in the hysteria scale ($t = 2.47$; $p < 0.05$) and in the depression scale ($t = 2.03$; $p < 0.05$) in subjects with low seriousness clinical intolerance compared to that ones with middle-high seriousness (figure 6 and 7). Moreover, we found that subjects with unlikely reactions ($n = 12$) have more hysterical traits than the others, as we can see in figure 8 ($t = 3.21$, $p < 0.01$).

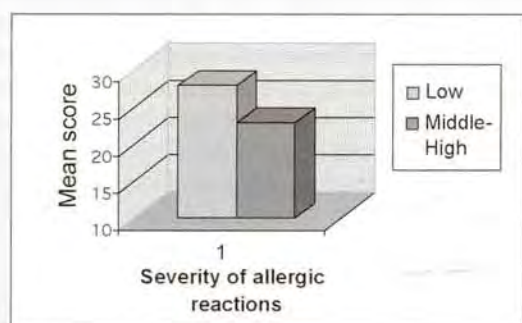


Figure 6: Mean scores in the Hysteria Scale accord to the severity of allergic reactions.

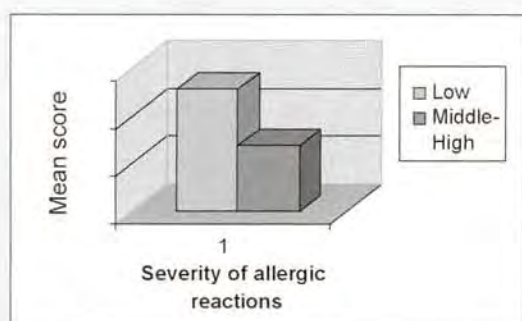


Figure 7: Mean scores in the Depression Scale accord to the severity of allergic reactions.

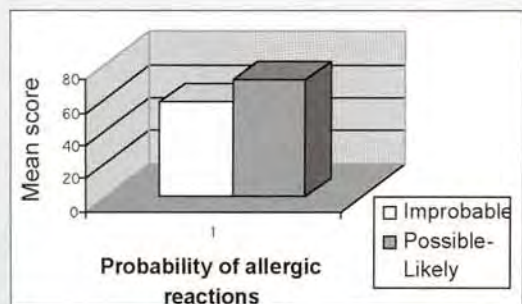


Figure 8: Mean scores in Hysteria Scale accord to probability of allergic reactions.

DISCUSSION

Drug intolerance reactions are very common events and can be life-threatening. It is unclear if psychological factors are antecedents or are the consequence of this particular kind of diseases. In the psychiatric Literature atypical drug responses, which are not due to drug allergy, have been considered as the outcome of factors associated with the variability of the organic substrate or the psychic apparatus in the drug-personality interaction (12). In a different perspective, Sansone (13) found that the prevalence of self-reported allergies to medication is not necessarily greater among patients with Borderline Personality Symptomatology, even if such patients may report a significantly greater number of allergies to medication, probably due to secondary gain and physiological sensitivity.

In our study we confirmed the prevalence of female sex in these disorders, particularly frequent in middle-aged married women (3). All the psychological variables considered presented in the whole sample a normal distribution, without any difference in relation to the sex. This seems to suggest that other factors may be responsible for the difference in prevalence of this pathology. Moreover, the majority of men in our group have a history of intolerance towards a single drug category, while women belong often to the group of the "multiple intolerant drugs patients", considering themselves as "allergic" to "all" drugs. Patriarca (2) studied this particular syndrome and conclude that an important psychosomatic component, together with hormonal, dysmetabolic, autonomic and disreactive factors could explain its pathogenic complexity.

Although the population considered in our study was less characterized, comprehensive of various kinds of patients, it was not expected that mean psychological scores would be clinically significant, because subjects were selected from non psychiatric population. However, considering the whole group of patients, the mean score of hysteria was lightly higher than normal: high scores in this scale may evidence deny, dependence style, seduction and fear of being refused by others. Another interesting result of the study is that 24% of subjects scored higher than the cut off for clinical depression, result fairly significant compared to the overall prevalence of depression in the general population evaluated by the same questionnaire, which is 12% (14). In recent studies performed on other groups of chronic patients, affected by bronchial asthma (15) and psoriasis (16), the frequency of depression results to be higher, respectively 33% and 48%. Finally, the analysis of the clinical variables considered in our patients showed that subjects with a history of less serious reactions and unlikely reactions were more depressed and hysterical.

The strategy to confirm the diagnosis of a suspected drug hypersensitivity should be rigorous and based on the anamnesis, physical examination, possibly followed by skin test, laboratory test and, ultimately, drug provocation or drug tolerance test. In some cases, clinical history is the only possibility to understand previous adverse drug reactions. In this situation, patient's feelings about the negative event are obviously very important and could strongly influence the response not only to the drug, but also to the placebo oral administration. Patients showing a reaction to the placebo represented in our study the 19% of the whole group: in these subjects we did not find any significant correlation with the Hysteria scale, as we had expected, nor with depression, suggesting the existence of different psychological characteristics influencing these reactions. Traditional testing of these patients is often difficult because of the anxiety level associated with the patient's past experiences and sometimes with other physician's behaviour. In fact, those subjects considering themselves allergic to all drugs, are often regarded as almost "untouchable", sometimes paroxystically, with the consequence of lack of prescription of any drug from other physicians.

Augustin et al. (17) found that patient education and relaxation treatment was effective only for a 24% of patients with drug hypersensitivities. This means that even if psychological and psychosocial support should be suggested to drugs intolerance patients, a psychological evaluation is necessary in order to identify the subgroup of patients to whom it may be indicated. In our opinion this double approach could be of great diagnostic value for the allergist, having also an important reassurance effect for the patient, to the aim of increasing the tolerance to subsequent drug administration.

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