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Parental anxiety and depression levels associated with challenge tests in children with suspected drug and food allergies

Şüpheli ilaç ve gıda alerjisi olan çocukların ebeveynlerinde provokasyon testleri ile ilişkili anksiyete ve depresyon düzeyleri

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Abstract

Aim: Oral food challenges (OFCs) and drug provocation tests (DPTs) are currently the gold standards for evaluating food and drug hypersensitivity, respectively; however, use of these tests on children may generate anxiety and depression among their parents. Our aim was to explore depression and anxiety level among parents of children who were undergoing clinical evaluation via a DPT or OFC.

Methods: This cross-sectional study included parents of patients diagnosed with food or drug hypersensitivity reactions in the pediatric allergy clinic between September 2018 and October 2019. Children in Group 1 were subjected to DPT, Group 2 underwent OFC, and Group 3 were healthy controls. Before a child underwent an OFC or DPT, all parents (one parent per child) completed the Hospital Anxiety and Depression Scale, which is a serial assessment for symptoms of depression and anxiety.

Results: The study included parents of 105 children, among which Group 1 (n=50 children) were subjected to DPT, Group 2 (n=35 children) underwent OFC, and Group 3 (n=20 children) were healthy controls. In all three Groups, parents were primarily female (62.9%). Anxiety and depression scores were significantly higher among the parents of children in Groups 1 and 2 *vs.* those of children in Group 3 (P=0.002 and P=0.028, respectively). Anxiety scores were significantly higher among parents of children in Group 2 than those of children in Group 1 (P=0.017).

Conclusions: DPTs and OFCs have a significant impact on the emotional status of parents. Parents of children with suspected or documented food allergy experience particularly elevated levels of anxiety and depression before an OFC.

Keywords: Oral food challenge, Drug provocation test, Parental, Anxiety, Depression

Öz

Amaç: Oral besin ve ilaç provokasyon testleri, günümüzde besin ve ilaç aşırı duyarlılığını değerlendirmek için altın standart testlerdir; ancak bu testlerin çocuklar üzerinde kullanılması ebeveynleri arasında anksiyete ve depresyon oluşturabilir. Amacımız, bir provokasyon testi aracılığıyla klinik değerlendirmeye giren çocukların ebeveynleri arasındaki depresyon ve anksiyete düzeylerini araştırmak idi.

Yöntemler: Bu kesitsel çalışmaya Eylül 2018 ile Ekim 2019 tarihleri arasında çocuk alerji kliniğinde gıda veya ilaç aşırı duyarlılık reaksiyonları tanısı alan hastaların ebeveynleri dahil edilmiştir. Çalışma çocukların ebeveynlerini içeriyordu; grup 1 DPT'ye, grup 2'ye OFC'ye tabi tutulan ve grup 3 sağlıklı kontrollerden oluşmakta idi. Bir çocuğa provokasyon testi uygulanmadan önce tüm ebeveynlerden (çocuk başına bir ebeveyn) depresyon ve anksiyete belirtileri için seri bir değerlendirme olan Hastane Anksiyete ve Depresyon Ölçeğini doldurmaları istenmiştir.

Bulgular: Çalışmaya 105 çocuk alındı, grup 1 (n=50 çocuk) ilaç provokasyonu yapılan, grup 2 (n=35 çocuk) besin provokasyonu yapılan ve grup 3 (n=20 çocuk) sağlıklı kontrollerdi. Her üç grupta da, ebeveynler esas olarak kadındı (%62,9). Grup 1 ve 2'deki çocukların ebeveynlerinde anksiyete ve depresyon puanları, grup 3'teki çocukların ebeveynlerine göre anlamlı olarak daha yüksekti (sırasıyla P=0,002 ve P=0,028). Grup 2'deki çocukların ebeveynlerinin anksiyete puanları, grup 1'deki çocuklarınkinden anlamlı derecede yüksekti (P=0,017).

Sonuçlar: Çocuğa yapılan ilaç ve besin provokasyon testlerinin ebeveynlerinin duygusal durumu üzerinde önemli bir etkisi vardır. Özellikle şüpheli veya belgelenmiş besin alerjisi olan çocukların ebeveynleri, besin provokasyon testi öncesinde, daha yüksek düzeyde anksiyete ve depresyon yaşarlar.

Anahtar kelimeler: Besin provokasyon testi, İlaç provokasyon testi, Ebeveyn, Anksiyete, Depresyon

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Introduction

Food allergy is a developing problem with a growing incidence in industrialized countries. Food allergies are estimated to have an impact on ~10% of children worldwide, which can result in a substantial deterioration in the quality of life of both the child and the family [1]. They can also be a source of significant morbidity and mortality [2].

It is well known that diagnosing children with food allergies can result in significant stress for parents [3]. Results of previous studies indicate that quality of life both the child and the families underwent deterioration if food allergy is suspected or diagnosed [4-7]. Interestingly, impaired quality of life due to food allergy has been shown to be more significant than that resulting from chronic diseases such as rheumatoid arthritis and diabetes mellitus [8]. The factors with direct impact on quality of life include the overall emotional impact as well as ongoing social, and dietary restrictions. When quality of life scores are low, all family members may experience symptoms of anxiety and/or depression [8].

Like food allergy, drug allergy is a widespread problem for practicing allergists. An incorrect diagnosis of drug allergy can result in the use of less effective and/or more expensive therapeutic modalities [9]. Drug provocation tests (DPTs) and oral food challenges (OFCs) are currently gold standards for diagnosis of suspected allergies; these tests can also be used to find safe alternatives for allergenic substances [10]. Previous studies showed that DPTs may cause a significant anxiety in adults with drug hypersensitivity, who underwent these tests [11]. Parents are routinely informed about the risks of these tests, which may result in increased anxiety.

Although anxiety associated with DPTs and OFCs has been reported [12-14], to the best of our knowledge, no studies that provide a quantitative assessment of parental anxiety and depression associated with these evaluations have yet been performed.

In the present study**,** our goal was to evaluate parental anxiety and depression symptoms related to the performance of these provocation tests in children with suspected food or drug allergies.

Materials and methods

Study design and participants

This study included parents of children who were diagnosed with food or drug hypersensitivity in our pediatric allergy clinic between September 2018 and October 2019. A total of 105 children and their parents (one parent per child) were enrolled in this study. Power analysis was performed before the initiation of the study to determine the minimum number of subjects that should be included in the patient and control groups. In this study, the required minimum sample numbers were determined as 60 patients and 15 controls (using Cohen criteria), alpha=0.05 and power=0.80. The number of subjects who were with both parents were 4 in Group 1, 3 in Group 2, none in the control Group. Five of them were mothers. Control Group was defined as patients who visited the general pediatrics polyclinics with any reason and agreed to be participants in the study. Demographic data and a detailed history of drug or food allergy (the type of reaction, duration and culprit drug/food and related phenomena...) were recorded for each child.

Exclusion criteria

The children who had a history of severe life-threating drug reactions (toxic epidermal necrolysis, Stevens-Johnson syndrome, drug rash with eosinophilia and/or acute generalized exanthematous pustulosis) were excluded from the study, as were parents with a past or current psychiatric history, including diagnoses of depression or anxiety. Also excluded were children who had an acute reaction within the previous 4 to 6 weeks, who used antihistamines and steroids on a regular basis, and who were diagnosed with another disorder, including urticaria, uncontrolled asthma, cardiac dysfunction, renal-hepatic disease or current upper airway infection.

Drug provocation tests

Provocations with the suspected drugs were performed according to the European Network for Drug Allergy Guidelines [15]. Reactions were classified as immediate if they were detected within the first hour of drug administration and non-immediate (delayed) type when responses were detected >1 hour after administration [16]. The children who experienced both immediate (urticaria, angioedema and anaphylaxis) as well as non-immediate reactions, (maculopapular exanthema) were included in the study. If the suspected reaction was compatible with drug hypersensitivity, skin provocation tests (prick and intradermal) with the suspected drug were performed according to guidelines. For diagnosis, skin tests were performed if a skin testing material was available. Skin testing was not performed in children with mild non-immediate skin reactions. Drugs that elicited reactions in the Group 1 patient cohort included antibiotics, paracetamol, ibuprofen, and macrolides.

Oral food challenges

OFCs were performed to confirm the diagnosis of a suspected food allergy or to determine whether tolerance has developed in children who have already been diagnosed. The OFC begins with a minimal challenge followed by incremental increases in dose provided in 20-minute intervals until the total challenge dose is reached and/or the child experiences an adverse reaction. Parents of children who experienced an immediate (urticaria, angioedema and/or anaphylaxis) or a nonimmediate reaction (maculopapular exanthem) were included in Group 2. OFCs were performed to detect responses to both immunoglobulin E (IgE) and non-IgE mediated food allergy [17]. Foods that elicited reactions among the children in Group 2 included cow's milk, egg, and banana.

Hospital Anxiety and Depression Scale

Parents (one parent per child) were evaluated by the Hospital Anxiety and Depression Scale (HADS), which is a series of standardized screening tests designed to identify symptoms of depression and anxiety. The HADS includes 2 subscales each with 7 questions that independently assess both anxiety and depression. For each question, parent participants were invited to indicate the best option related to their emotional state on a scale from 0 to 3; the participants were permitted only one response for each question. The cutoff points for the Turkish population include Hospital Anxiety and Depression Scale-Anxiety (HADS-A) scores of 10/11 for anxiety and Hospital

Anxiety and Depression Scale-Depression (HADS-D) scores of 7/8 for depression [18].

Statistical analysis

Statistical analyses were performed using SPSS statistical software version 21 (SPSS Inc, Chicago, Illinois). Continuous data are presented as mean ± standard deviation. The Shapiro–Wilks test, histogram graphics, skewness and kurtosis values were examined to determine normal distribution. Mann–Whitney U test was used to compare two groups for non-normally distributed variables and the Kruskal–Wallis H test was used to compare more than two Groups. Categorical data from patient and control groups were compared using the Chi-Square test. Pearson correlation test was used to determine correlation in normally distributed groups. If not normally distributed, Spearman correlation test was used. A value of $P \leq 0.05$ was considered statistically significant.

Results

Study groups

The study groups included the parents of patients in Group 1 (DPT, n=50 children), parents of patients in Group 2 (OFC, n=35 children) and parents of children in Group 3 (healthy controls, n=20 children). There were no significant differences with respect to age of the child, age of the parent, gender, educational statuses, or occupation of the parents associated with each of the three groups ($P>0.05$). Demographic characteristic of patients in Groups 1 and 2 as well as the controls (Group 3) are included in Table 1. Parents of the children were primarily female in all three Groups (62.9%).

Evaluation of the children for drug allergies

The mean age (SD) was 5 (3.2) years for children and 35 (5.2) years for parents. Drug provocation testing was negative in 47 of the 50 children (94%) in Group 1. Of these, 20 children (40%) underwent DPT, 27 (54%) underwent both skin tests and DPTs, and 3 (6%) underwent skin tests alone. The most common etiologic agents were β-lactam antibiotics (62%) followed by paracetamol (12%) and ibuprofen (12%). The clinical presentations included cutaneous reactions in 38 (76%), and anaphylaxis in 12 (24%) of the children in Group 1. Responses including urticaria with or without angioedema were identified in 28 (56%) as the most common symptoms and immediate reactions were higher among those reporting hypersensitivities to antibiotics than to any other drugs ($P=0.001$).

Evaluation of the children for food allergies

The mean age (SD) was 5 (2.5) years for children in Group 2 and 34 (4.9) years for their parents. Cow's milk (74.2%) was the most common cause of hypersensitivity reactions followed by hen's egg (22.8%). Cutaneous symptoms were the most common reactions reported by those in Group 2 before OFC (n=27, or 77.1%). Anaphylaxis was observed in 8 children (22.8%). Time between the reaction and formal evaluation for allergy was 4(7) months. With respect to this parameter, there were no significant differences between the findings of Group 1 and Group 2 ($P>0.05$).

Positive challenge tests

Forty-seven (94%) children had negative responses to tests for drug allergy; 3 children (6%) responded positively. Similarly, thirty-four (97%) children had negative responses to food challenge; only one child (3%) had a positive result. Antihistamine therapy was used in patients who developed an allergic reaction to a food or drug; epinephrine was not required. Given the very few positive results to challenge tests, we eliminated this group from statistical analysis. A DPT was performed in 54% of the children in Group 1 for diagnostic purposes; 46% of the tests were performed to identify suitable alternative agents. The OFC was performed in 77.5% of the children in Group 2 for diagnostic purposes and in 22% to identify alternative agents. The DPTs performed to identify alternative agents typically used cephalosporins (18%). Most OFCs for diagnostic purposes were performed using cow's milk (54.2%).

Table 1: Demographic characteristics of patients and the control group

	Group 1 (DPT) n(%)	Group 2 (OFC) n(%)	Group 3 (Control) n(%)	*P*-value
Children				
Female	25(50)	16(45.7)	11(55)	0.799[b]
Male	25(50)	19(54.3)	9(45)	
Age (years)				
Mean (SD)	5(3.2)	5(2.5)	6(4)	0.66[a]
Parents				
Mother	30(60)	23(65.7)	13(65)	
Father	20(40)	12(34.3)	7(35)	0.845[b]
Age (years)				
Mean (SD)	35(5.2)	34(4.9)	35(4.1)	0.631[a]
Occupation				
Homemaker	25(50)	18(51.5)	11(55)	0.999[b]
Clerk	12(24)	8(22.9)	5(25)	
Office worker	10(10)	7(20.0)	3(15)	
Others	3(6)	2(8.6)	1(5)	
Education level				0.959[b]
Elementary education	10(20)	7(20)	5(25)	
High school	17(34)	14(40)	7(35)	
College	23(46)	14(40)	8(40)	
Total	50(100)	35(100)	20(100)	

[a] Kruskal Wallis H Test, [b] Pearson (Exact) Chi-Square Test

Assessment of parental depression-anxiety levels

The mean scores of parents who completed the Hospital Anxiety and Depression Scale are summarized in Table 2. Both HAD-A and HAD-D mean scores were significantly higher among the parents of children in Groups 1 and 2 than among those of children in the control Group ($P=0.002$ and; $P=0.028$, respectively). Also HAD-A scores were significantly higher in Group 2 than Group 1 ($P=0.017$). Mothers' anxiety level was higher than fathers' ($P=0.03$). HAD-A and HAD-D scores were significantly higher in the parents of children who had a history of anaphylaxis in both Groups 1 and Group 2 ($P=0.01$). No statistical difference was found between the groups in the tests performed to find diagnostic or alternative agents in terms of parents' HAD-A and HAD-D scores ($P>0.05$).

We compared mothers' (n=53) and fathers' (n=32) HAD-A and HAD-D scores. There were no significant differences between mothers' and fathers' HAD-A and HAD-D scores ($P=0.433$ and $P=0.777$ respectively) (Table 3). It was found that HAD-A and HAD-D scores were correlated with each other ($P<0.01$ and r:0.606) but not correlated with parental age, time to allergy work up and child age (Table 4).

Table 2. The mean scores of parents in the Hospital Anxiety and Depression Scale

	Parents of Group 1 (DPT) (n=50)	Parents of Group 2 (OFC) (n=35)	Parents of control Group (n=20)	*P* df	Comparison pattern
HADS-Anxiety Mean(SD)	5.82(4.14)	8.20(3.37)	4.83(2.85)	0.002[c] 2	0.002[a] 0.017[b]
HADS-Depression Mean(SD)	5.00(3.80)	5.85(2.83)	3.63(3.01)	0.028[c] 2	0.027[a]

HADS: Hospital Anxiety and Depression Scale *, [a] Comparison pattern indicates the standardized mean difference between Group 2 and Group 3, [b] Comparison pattern indicates the standardized mean difference between Group 1 and Group 2, [c] Kruskal- Wallis

Table 3: Comparison of fathers and mothers' HAD scores

	Fathers (n=32)	Mothers (n=53)	Total (n=85)	*P*-value
HADS-Anxiety Mean(SD)	5.00(0.67)	5.66(0.50)	5.41(3.68)	0.433[a]
HADS-Depression Mean(SD)	4.41(0.67)	4.45(0.47)	4.44(3.54)	0.777[a]

[a] Mann-Whitney U test

Table 4: Correlation test of variables

	Child age (r)	Parental age (r)	Time between reaction and allergy work- up (r)	HADS-A	HADS-D
HADS-A	0.162	0.160	-0.119	1	0.606[a]
HADS-D	0.185	0.065	0.023	0.606[a]	1

[a] Spearman's rho test

Discussion

The results of the current study indicate that the parents of children with suspected food allergy have higher anxiety and depression scores before OFC. In our study, the anxiety and depression levels of parents of the children with suspected drug allergy were higher than healthy controls' parents but lower than those with suspected or documented food allergy. The reasons may include the presence of fewer opportunities to encounter agents that elicit drug-related allergic reactions, and the fact that they are more easily managed than allergies to food substances. This information may decrease anxiety and depression levels in parents of children with suspected drug allergy. There might be many reasons to explain the differences regarding children's individual characteristics, family characteristics, previous medical history, and life events. One study compared the anxiety and depression levels with HADS of the mothers of children with suspected food allergy on the first clinical visit and second visit after 4–6 weeks [19]. The study reported no higher anxiety and depression scores; however, the children were not evaluated by OFC and the parents were evaluated during two visits only. The studies related to anxiety of parents of the children with suspected food allergy have been compared before and after OFC. The parents' anxiety level decreased after OFC [12-14].

In a randomized controlled adult study, it was aimed to define placebo reactions during DPT, the subjects' anxiety and depression symptoms were evaluated by HADS before DPT. It was shown that HADS positivity before the test was correlated to placebo reactions. It was recommended that evaluating psychiatric symptoms before DPT was important to define placebo reactions [20].

Anxiety and depression scale scores can differ between parents of an individual child [21,22]. King et al. [22] found that mothers of children with food allergies express more anxiety and stress than the fathers. Another study reported that the mothers of children with food allergy reported higher levels of impairment with respect to quality of life than did fathers, regardless of the type or severity of the allergy or the existence of comorbidities [14]. Knibb et al [23]. reported that the mothers experienced comparatively prominent levels of anxiety prior to an OFC. Not the only suspicion of food allergy, but the actual performance of the OFC may increase parental anxiety levels. However, quality of life of the families was positively affected by having access to clear-cut results [23].

Most of the parents involved in our study were mothers (62.9%); overall, their anxiety level was higher than that of the fathers. The findings were consistent with the literature [12,22,23]. Beken et al [12]. reported that the mothers of children with suspected food allergy had higher anxiety before OFC than the mothers of healthy control children. Parents' reactions to any condition impact children's feelings and behavior, and parental anxiety and depression level may impact compliance to the tests. Mothers typically play a larger role in caring for children, including making decisions on medications, preparing food, reading labels, and related activities, all of which may cause their anxiety levels to increase [22]. Thus, mothers of children who were to undergo challenge tests might be more anxious and depressive than the fathers. In our study, there were no significant differences between anxiety and depression scores of fathers and mothers. However, due to the difference in the number of mothers visiting the clinic, gender differences could not be determined.

To the best our knowledge, this is the first study which evaluates parents' anxiety and depression level before DPT that are performed to children with suspected drug allergy.

Limitations

The first limitation of this study is the fact that we did not reevaluate and compare anxiety and depression scores of the parents sometime after the results of these provocation tests. The second limitation is the lack of comparison of parents with same gender. It must be considered that there are differences between with mothers' and fathers' anxiety and depression level. The third limitation is that we did not evaluate parents' physical and mental health problems, children's' mental health and other medical problems, family relationship quality, family functioning and other familial or individual factors that may affect depression and anxiety levels. Further larger and well-controlled observational studies are required in the future to consolidate the association between parental anxiety-depression and challenges.

Conclusion

We determined that the anxiety and depression scores of parents whose children require DPT or OFC testing are uniformly high regardless of the test type. Parents' anxiety and depression level were higher when parents were informed about the risks of these tests. However, informing parents that DPT will reveal alternative agents decreases their anxiety and depression levels. It may be useful to limit parents' anxiety before any type of allergy-provocation test, as that will increase compliance with both the test and the treatments offered.

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