Depression and anxiety among parents of phenylketonuria children

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ABSTRACT

Objective: To investigate the existence of depression and/or anxiety with underlying risk factors among parents of children with classical phenylketonuria (PKU).

Methods: This cross-sectional study was conducted in the Division of Pediatric Metabolism, Ankara Children’s Hospital, Dokuz Eylul University, Kirkkale University, and Erzurum Local Research Hospital, Turkey, between January and July 2014.

Results: Depression and anxiety scores were significantly higher in the case group (BDI: 12.3±9.1; STAI-S: 38.2±9.6; STAI-T: 43.2±6.9) than controls (BDI: 5.4±4.1 p=0.000; STAI-S: 31.8±7.6 p=0.001; STAI-T: 37.0±7.2 p=0.000). Mothers of the patients had higher scores than the other parental groups (BDI: p=0.000, STAI-S: p=0.001 and STAI-T: p=0.000). Logistic regression analysis showed that low educational level of the parent was the only independent factor for depression (OR: 9.96, 95% CI: 1.89-52.35, p=0.007) and state anxiety (OR: 6.99, 95% CI: 1.22-40.48, p=0.030) in the case group.

Conclusion: A subset of parents with PKU patients have an anxiety or depressive disorder. Supportive services dealing with the parents of chronically ill children such as PKU are needed in order to reduce the level of anxiety.

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Phenylketonuria (PKU, OMIM: 261600) is an autosomal recessive disorder caused by hepatic phenylalanine hydroxylase enzyme (EC 1.14.16.1) deficiency. Phenylketonuria is the most prevalent inborn error of amino acid metabolism in the world. There is a nationwide newborn screening program in Turkey since 2007 for this disease. If PKU is not diagnosed at birth and dietary treatment was not started, it can cause severe irreversible mental deterioration. Treatment of classical PKU depends on lifetime phenylalanine (Phe) restricted diet with supplementation of Phe-free amino acid mixtures to maintain therapeutic blood Phe levels and adequate nutrition. Several studies showed that discontinuation of the therapy or diminished compliance to this strict diet resulted in neuropsychological problems as well as decline in intelligence quotient (IQ), even though the diet was started during the neonatal period.1-3

Successful treatment of classical PKU, like other disorders of inborn errors of metabolism (IEM), requires a team effort including physicians with other health workers, particularly patients and their parents.4,5 Parents have to supervise and evaluate the daily nutritional intake of their child continuously.6 The major problem encountered in the treatment of PKU in developing countries is the lack of dietary adherence, which is due to limited number of experienced clinics, large families, ignorance of the parents, financial limitations, low risk perceptions of the parents, difficulties in the supply of low-protein products.7-9

As in PKU, diet-related diseases such as diabetes, celiac disease, food allergies, cystic fibrosis, and other inherited metabolic diseases were shown to be associated with the increased risk of anxiety and depression both in patients10,11 and their families due to the decreased quality of life within the household.11-14 Decreased quality of life and presence of mood disorders in PKU patients has been largely investigated in different studies.15-17 However, there are few studies investigating mood disorders in parents of PKU patients in the literature.6,12,18 Caring for a chronically ill child with or without disabilities at home might be somewhat disconcerting for the caregivers. The development of interventions to reduce the stress experienced by caregivers is necessary for the success of the dietary treatment of PKU patients. Determination of predictors of depression and anxiety among parents caring for PKU children may help health professionals in identifying those parents who need special attention to restore their psychological well-being. The objective of this study was to investigate the existence and severity of depression and anxiety in parents of children with classical PKU and to evaluate the relationship between mood disorders and possible risk factors in those parents.

Methods. Study population. This cross-sectional descriptive study was conducted in the Divisions of Pediatric Metabolism, Ankara Children’s Hospital, Ankara, Dokuz Eylul University, Izmir, Kırıkkale University, Kırıkkale and Erzurum Local Research Hospital, Erzurum, Turkey between January and July 2014. Among 65 eligible families, 4 parents refused to participate due to unsuccessful contact. The respondents and non-respondents did not differ according to demographic features of the families. A total of 61 patients and 36 healthy controls with similar demographic characteristics were enrolled in the study.

All the patients were diagnosed with a classical PKU (all >1200 µmol/L with normal dihydropteridine reductase activity). Most of them have been started their diet during the newborn period and were on Phe-restricted diet for at least one year. Five of the children were diagnosed at the second months of life and started the diet. The exclusion of this study were patients who were using BH4 (sapropterin dihydrochloride) or large neutral amino acid medications, while most patients were receiving 0.20-0.40 g/kg/day natural protein with their diet; hyperphenylalaninemia patients with free diet; parents who had a chronic disease requiring dietary or medical treatments or having a child with chronic or acute disorder other than PKU. Families, who left some questions blank were also excluded from the study also.

Procedures. We searched the PubMed database for articles using the following keywords “phenylketonuria, depression, anxiety, diet, inborn errors of metabolism, parent, mother, father” to reach the previous studies on this topic and to decide the methods of the study. After describing the materials’ content and the study protocol to the parents, one of them (mother/father) was asked to complete the questionnaires. Only one of the parents completed the scales. If the patient was taken to hospital with one of the parents, that parent became the person who completed the scales. When the patient was taken with both of the parents, the parent who became volunteer to complete the scales was selected. This took approximately 25-30 minutes.

Scales used in the study. We prepared the questionnaire and 3 sections were considered. First section was on the sociodemographic characteristics of the child and the family (children’s age, gender and dietary compliance, parent’s age, gender, marital status, educational level, occupation). The second section was on the stressors affecting the family such as illnesses, experience of financial troubles due to household income, history of medical or psychiatric disease or
drug usage, domestic losses and family problems. The third part was on the supply of specific formulas and low-protein products, experiences, and interactions with medical staff and their satisfaction.

**State-Trait Anxiety Inventory (STAI-S and STAI-T).** This is a self-report questionnaire consisting of 2 sub-scales each including 20 items evaluating the level of anxiety. The Turkish validity and reliability studies were performed by Oner and le Compte in the Turkish adult population. State anxiety describes the person's feelings at a particular time and under particular conditions, whereas trait anxiety is independent of conditions and reflects personality characteristics and general feelings. The responses to each item in the anxiety questionnaire are given a score from 1 to 4. The total scores can be in range from 20 (lowest possible anxiety score) to 80 (highest possible anxiety score), with higher scores indicating more anxiety. Although no cut-off indicating clinically significant levels of anxiety is established in the technical or administrative materials for the STAI, cut-offs of 40 and 45 were used in prior studies. In our study, the scores ≥45 for STAI-S was accepted as the presence of state and STAI-T was accepted as the presence of trait anxiety.

**Beck Depression Inventory (BDI).** This inventory consists of 21 items, each rated on a 0-3 point Likert scale, and reflects the presence and severity of depression. The questions of the inventory represent symptoms commonly associated with a depressive disorder such as mood, crying spells, guilt, self-hate, sleep and appetite disturbances, and weight loss. The highest score of this scale was 63 and the high total scores indicate a high severity level of depression. The Turkish validity and reliability studies of this inventory were performed by Hisli. The cut-off score for BDI was 17.

**Ethical approval.** The study protocol was designed in compliance with the Declaration of Helsinki. Informed consent was obtained from patients’ parents on enrollment in the study. The study was started after the approval of the Ethics Committee of Ankara Children’s Education and Research Hospital.

**Statistical analysis.** Statistical analyses were performed using the Statistical Package for Social Sciences Version 12.0 (SPSS Inc., Chicago, IL, USA). Values were expressed as mean±SD or as percentages. The Kolmogorov-Smirnov test was used to assess the normality of samples distribution. Kruskal-Wallis test was used to compare the means among 4 groups. The mean was compared by using the Student’s t-test or Mann-Whitney U-test. The percentage was calculated in the presence and absence group by Pearson’s Chi-square test. Correlations between independent parameters were computed through the bivariate Pearson’s correlation analysis. Correlation between continuous variables were categorized as low (correlation coefficient was between 0.10–0.29), moderate (between 0.30-0.49) and high (>0.50) according to their correlation coefficient values. To identify the independent variables (neurological impairment of the patient, gender and educational level of the parents, and the difficulties in the supply of low-protein products due to the poverty) that contribute to depression and anxiety, multiple logistic regression analysis was performed and values were expressed as odds ratios (ORs) and 95% confidence intervals (CIs). The limit of statistical significance was set at p-values <0.05.

**Results.** The sociodemographic characteristics of the patients and controls are presented in Table 1. There were no significant differences between the case and the control groups regarding the children’s age and gender, parental age and gender, the educational level of the parents and number of children in the family (Table 1). All parents were married and there were no divorced parents in both groups.

Depression and anxiety scores were significantly higher in the case group than controls (Table 2). Mothers of PKU patients had significantly higher depression, and trait- and state anxiety scores compared with the other parental groups (Table 3). Fathers of control children had significantly lower trait anxiety scores compared with the other groups (Table 3).

Seven parents had more than one PKU patients at home (2 families had 3 children and 5 families had 2 children with PKU). Number of affected children in the family, age and gender of the patient were not related with the depression or anxiety scores of the case group. There was no correlation between parental anxiety and depression scores and patient’s age (Beck: r = -0.158, p=0.258, STAI-S: r=0.173, p=0.178, STAI-T: r=0.182, p=0.111). Parents with lower educational level had significantly higher depression and anxiety scores in the case group (Table 4). Parents with mentally retarded children had significantly higher Beck (21.0±8.9) and STAI-S scores (46.7±7.0) than the parents of neurologically unaffected PKU patients (10.2±7.9, p=0.001) and STAI-S scores (36.3±9.1, p=0.001). The State-Trait Anxiety Inventory scores were 47.3±7.2 in mentally retarded group and 42.2±6.4 in unaffected group and there were no significant differences between the 2 groups (p=0.062). Fourteen (22.9%) of 61 PKU patients had 2 unemployed parents and their family income consisted of state aid. The vast majority (42 families, 68.8%) of families stated that it was a financial burden to supply of low-protein products because of
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inadequate or absent health insurance. Parents who failed to provide low-protein products had significantly higher Beck (14.2±9.0), STAI-S (41.5±8.9), and STAI-T scores (44.8±6.3) than parents who easily provided low-protein products (Beck [7.2±7.6] p=0.004, STAI-S [31.2±7.6] p=0.000, and STAI-T scores [39.4±6.5] p=0.01).

In the case group, the parental depression score was positively correlated with STAI-S (r=0.523, p=0.000) and STAI-T scores (r=0.440, p=0.001). As expected, STAI-S score was correlated with STAI-S score (r=0.516, p=0.000).

Many parents (58 parents, 95%) reported that their interactions with medical staff were excellent. Logistic regression analysis revealed that lower educational level of the parent was the only independent factor for parental depression (p=0.007) and state anxiety (p=0.030). Gender of the parent, difficulty in the supply of low-protein products and presence of mental retardation of the children were not independent risk factors for depression and anxiety in this model (Table 5).

**Discussion.** Depression and anxiety scores of PKU patient parents were higher than the parents with healthy children. Moreover, mothers of these patients had significantly higher depression and anxiety scores than fathers. Parents with low educational level had higher depression and anxiety scores than parents with higher educational degree. Diet restrictions for the diseases have some difficulties that impact social life. The limits caused by the strict diet and the potential risk of mental retardation makes PKU a burden for patients and their families, affecting their quality of life.

### Table 1 - Demographic data of the phenylketonuria patients and healthy controls.*

| Demographic data | PKU patients n=61 | Healthy controls n=36 | P-value |
|------------------|-------------------|-----------------------|---------|
| Child's age (years) | 6.5±5.4 | 6.6±4.8 | 0.654 |
| Child's gender (M/F) | 32/29 | 19/17 | 0.768 |
| Parental age (years) | 34.3±5.8 | 35.9±6.7 | 0.244 |
| Parental gender (M/F) | 18/43 | 7/29 | 0.340 |

**Mother's education n (%)**

- Elementary/high school: 26 (40.5) vs 12 (41.4) (p=0.150)
- College/university: 17 (39.5) vs 17 (58.6) (p=0.637)

**Father's education n (%)**

- Elementary/high school: 5 (27.8) vs 1 (14.3) (p=0.637)
- College/university: 13 (72.2) vs 6 (85.7) (p=0.742)

### Table 2 - Mental disorders and current State-trait anxiety inventory (STAI) and Beck depression inventory (BDI) scores of parents of the phenylketonuria (PKU) patients and healthy controls.

| Scores | PKU patients n=61 | Healthy controls n=36 | P-value |
|--------|-------------------|-----------------------|---------|
| Previous or current mental disorders of participants n (%) | 5 (9.1) | 0 (0) | 0.000 |
| BDI score | 12.3±9.1 | 5.4±4.1 | 0.000 |
| STAI-S score | 38.2±9.6 | 31.8±7.6 | 0.001 |
| STAI-T score | 43.2±6.9 | 37.0±7.2 | 0.000 |

BDI - Scores of Beck depression, STAI - State-trait anxiety (*Kruskal Wallis test, †patients' mother versus other groups, p<0.05 (Mann-Whitney U-test); ‡healthy controls' father versus other groups, p<0.05 (Mann-Whitney U-test))

### Table 3 - Scores of Beck depression and STAI inventories of parents of patients and healthy controls.

| Scores | PKU patients | Healthy controls | P-value* |
|--------|--------------|------------------|---------|
| BDI | 13.6±8.6† | 9.1±9.7 | 0.000 |
| STAI-S | 39.8±8.5† | 34.5±11.2 | 0.001 |
| STAI-T | 44.4±6.7† | 40.0±6.3 | 0.000 |

BDI - Scores of Beck depression, STAI - State-trait anxiety (*Kruskal Wallis test, †patients' mother versus other groups, p<0.05 (Mann-Whitney U-test); ‡healthy controls' father versus other groups, p<0.05 (Mann-Whitney U-test))

### Table 4 - Association of parental education levels and STAI and BDI scores in phenylketonuria group.

| Scores | Education levels of the parents | P-value |
|--------|---------------------------------|---------|
| Elementary/high school | 16.8±9.5 | 7.5±5.8 | 0.000 |
| College/university | 42.1±10.1 | 34.3±7.4 | 0.001 |
| STAI-S | 45.3±7.1 | 41.0±5.9 | 0.025 |

STAI S-T - State-Trait Anxiety Inventory S-T, BDI - Scores of Beck depression

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*All parents were married; marital status was not included, M-male, F-female, PKU - phenylketonuria
life, and psychosocial well-being. Dietary restriction makes the diet “monotonous.” A “monotonous diet” of one family member was shown to restrict all family members feeding style, which could be one of the reasons of the maternal anxiety. In addition to this highly restrictive diet, possible factors contributing family stress may include restriction of daily activities, cognitive disabilities and learning problems of patient, regular hospital visits and frequent blood sampling procedures for monitoring Phe levels and lastly, financial problems.

One of the most striking results of this study was the significantly higher depression and anxiety scores of mothers than fathers of the PKU patients. Similarly, in previous studies, it was found that mothers had worse psychological and physical quality of life and higher anxiety and stress levels than fathers of children who treated with restrictive diet. Suffering from a chronic metabolic disease with the necessity of caregivers control of patient’s diet often results in overprotection of patients by their parents. On the other hand, mothers traditionally have greater role in buying and preparing foods and therefore, to be a primary coordinator of family’s sick child makes the mother more stressful and anxious compared with other family members. Fathers often spend a significant part of their day at work (out of home) and possibly feel less disease-specific parenting stress compared with mothers. Children’s neurological impairment was found to be another important predictor of the parents’ depression and anxiety in our study. Previous studies detected higher levels of anxiety and depression scores of parents who had mentally disabled children when compared with controls. Moreover, more severe forms of retardation were related with higher levels of anxiety in the caregivers, especially in mothers. This association is caused by the child dependency on the mother for daily activities of children, for example, toileting, bathing, feeding, clothing and transport. Besides all these intensive activities, preparing the highly restrictive diet increases the maternal caregiving hours and affect the quality of life in families with a PKU patient. In addition, the caregiver’s awareness on the irreversibility of the mental retardation of their sick child is another important causative factor for the parental stress.

Difficulties in the supply of low-protein products due to the low economical status of the family could be another important stress-related factor in our study. Management of a PKU patient is both time-consuming and expensive for the family, even in developed countries. Low-protein food products are indispensable part of the PKU diet and they responsible 99% of this extra expenditure. Only Phe-free formulas are paid totally by our health insurance system, therefore, all families with moderate to low income are under pressure on the supply of other specific dietary requirements of their children, because of very limited reimbursement of these products. In our study, low educational level of the parents was associated with higher depression and anxiety scores. Moreover, logistic regression analysis showed that a decrease in the literacy level was the only independent factor for depression and anxiety in parents of PKU children. Low educational level was found to be associated with the increased stress and depression rates both in general population and in caregivers of sick child. Moreover, educational and cultural factors of the parents were also shown to be the main determinants of dietary compliance and good clinical outcomes in children with PKU in some studies. Relationship between educational degree and mood disorders is important especially in women. Previous studies have shown that, because of having fewer socioeconomic resources such as power, authority and earnings, women appear to be especially dependent on education for emotional well-being. In our study, most of the responders was consisted of mothers (43 mothers, 70.4%), therefore our results were compatible with the literature. Parental education is related with multiple sources of psycho-social support, positive home environments, particularly more positive and sensitive parenting, which are likely to be protective against depression.

### Table 5 - Logistic regression analysis between risk factors for the presence of depression, state- and trait anxiety in phenylketonuria group. CI - confidence interval, OR - odds ratio

| Variables                      | Depression       |  | State anxiety    |  | Trait anxiety   |  |
|-------------------------------|------------------|---|------------------|---|-----------------|---|
|                               | OR (95% CI)      | P-value | OR (95% CI)      | P-value | OR (95% CI)      | P-value |
| Education level of the parent | 9.96 (1.89-52.35)| 0.007   | 6.99 (1.22-40.48)| 0.030 | 1.16 (0.34-3.96) | 0.811   |
| Presence of mental retardation| 4.29 (0.87-20.39)| 0.073   | 5.17 (0.94-28.44)| 0.059 | 2.71 (0.66-11.05)| 0.162   |
| Difficulty in the supply of low-protein products due to the poverty | 2.25 (0.36-14.08)| 0.383 | 2.18 (0.45-14.12)| 0.298 | 1.49 (0.40-5.47) | 0.547   |
| Gender of the parent          | 0.79 (0.12-5.23) | 0.810 | 0.42 (0.03-4.69) | 0.485 | 3.63 (0.89-14.78)| 0.071   |
This study has some limitations. Firstly, the evaluations depended on self-reported questionnaires and scales, and lacked clinical interviews. A second limitation was the relatively small sample size of the patients and control groups. Therefore, the results should be regarded as preliminary. Another limitation was the cross-sectional nature of the study. A prospective study can be made for showing the mood status of same parents in different age periods of their children. Lastly, we did not compare both fathers and mothers of each patients for mood disturbances. New studies that investigate the intraclass comparison between mothers and fathers are needed. However, its strength is that; it can represent Turkey as it was conducted in 4 different regions of this huge country.

In conclusion, a subset of parents of children with PKU have an anxiety or depressive disorder. These findings add to the literature’s surrounding cultural, social, and various differences such as age and gender in parental anxiety, and provide a basis for future research to identify the need for early preventive measures to combat the emotional and behavioral difficulties experienced by families of PKU patients. Although there is no consensus on how to manage PKU patients parents’ anxiety and depression, it is essential that the health care team should establish a supportive and continue therapeutic communication with families. In the light of the results of this study, a future study in order to explain and specify the origin of these difficulties should be conducted. On the other hand, regional services endowed with health staff aware of the cultural and environmental characteristics of the province should be established in order to support parents in surmounting difficulties of this chronic disease.

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