The Struggle That Is Phenylketonuria : What Do The Patients and Caregivers Suffer From

Abstract

Objective: To assess the stress levels and life hardships of phenylketonuria patients and their parents.

Study Design: Between January 2020 – June 2020, a total of 156 phenylketonuria patients and their parents who arrived for their regular examinations were included. Parents were asked to fill the parenting stress index, Zarit burden scale and the strengths and difficulties questionnaire and children over the age of eleven were asked to fill the Rosenberg self-esteem scale, the stait-trait anxiety inventory and strengths and difficulties questionnaire.

Results: We found a significant negative correlation between Rosenberg self-esteem scale and age at diagnosis, (r=-.27, p=.035), age of the mother (r=-.33, p=.009) and age of the father (r=-.38, p=.004). There was a significant positive correlation between the stait-trait anxiety inventory and age of the patient, (r=.36, p=.006) , age of the mother (r=.29, p=.031) and age of the father (r=.38, p=.024). In child form of strengths and difficulties questionnaire ; emotional problems part was significantly positively correlated with serum phenylalanine levels at diagnosis (r=.35, p=.036); total points were significantly positively correlated with serum phenylalanine levels at clinical examination (r=-.34, p=.004) and social problems part was significantly negatively corelated with the age of the father (r=-.34, p=.047). We found a significant positive correlation between Zarit burden scale and number of siblings (r=.195, p=.023). In parent form of strengths and difficulties questionnaire; emotional problems part was significantly positively correlated with age of the patient (r=.217, p=.032), peer problems part was significantly positively correlated with age at diagnosis (r=.211, p=.037), behavioral problems (r=.203, p=.045) and attention deficit and hyperactivity (r=.203, p=.045) parts were significantly positively correlated with serum phenylalanine levels at diagnosis.

Conclusions: Phenylketonuria is hard to cope with both for the patients and their parents because of diet obligation, high expenditures for the formulas required for the diet, requirement of regular clinical examinations and possible development of mental disability and psychiatric disorders Patients and their families should be psychologically evaluated and support should be provided if needed.

Keywords: Phenylketonuria, stress, caregivers burden

List of Abbreviations:

Phe: Phenylalanine
BH_4 Tetrahydrobiopterin
PAH Phenylalanine Hydroxylase
PKU Phenylketonuria
TAI Trait Anxiety Inventory
SAI Stait Anxiety Inventory
SDQ Strengths and Difficulties Questionnaire
ADHD Attention Deficit and Hyperactivity Disorder

Introduction

Phenylalanine is an essential aminoacid. It's required for protein production and cell function in human body. Thyroxine production is also dependant on phenylalanin intake since it's synthetised in liver from phenylalanine in a reaction catalysed by enzyme "Phenylalanine Hydroxylase" . [1] Therefore disruptancies in enzyme functions cause phenylalanine abundance. Phenylalanine accumulates in body (especially in central nervous system) and it's excreted by kidneys as fenylpiruvic acid. [2]

This abundance of phenylalanine is called hyperphenylalaninemia and blood levels help define the borders of the disease. Biochemical definition is blood phenylalanine level above 2 mg/dl (120 µmol/L) but clinical spectrum is wide and symptoms become worse as levels rise. [3] Deficiency of the Phenylalanine Hydroxylase (PAH) enzyme (EC 1.14. 16.1)causes the illness which has come to known as *Phenylketonuria* (OMIM #261600) and the urinary products give urine the specific musty odor. Phenylketonuria (PKU) has autosomal recessive inheritance pattern and PAH gene is located on 12q23.2. [4] This genetic inheritance pattern causes increased number of patients in countries where consanguineous marriage is common – such as Turkey. Frequency of phenylketonuria is 1 in every 4.000 children in Turkey as opposed to Europe where it's 1 in every 10.000 children. [2,5-8]. As misfortunate as it is, this facilitates observation of the disease and the hardships it brings.

The severity of clinical spectrum is dependant on blood levels of phenylalanine. Therefore the disease classification is made according to phenylalanine measurements. Blood levels between 2 and 6 mg/dl is defined as mild hyperphenylalaninemia, 6-10 mg/dl as mild phenylketonuria, 10-20 mg/dl as moderate phenylketouria and levels above 20 mg/dl is defined as classical phenylketonuria. [2,9] Disorders of tetrahydrobiopterin (BH_4) metabolism which is the coenzyme of PAH, causes BH_4 responsive hyperphenylalaninemia. [10]

The most important factor in the treatment of phenylketonuria is phenylalanine-restricted diet, and this treatment should be lifelong. The aim of the treatment is to keep the blood phenylalanine level within the recommended range, 6 mg/dl limit is accepted for children aged under 12 years , 10 mg/dl limit is accepted for children and adults aged 12-18 years. [11] For this purpose, blood phenylalanine levels should be measured at regular intervals, physical examination evaluations and clinical follow-ups are required in order to monitor the dietary compliance of the patients. Apart from diet, some patients can have a partially or completely normal diet by taking the pharmacological agent containing tetrahydrobiopterin orally. [12]

Reasons such as emotional strain on food restriction, difficulty in giving the child the appropriate diet due to the social pressure, difficulty in obtaining dietary products because of high costs, and difficulty in complying with the diet in social gatherings make dietary continuity difficult. [13] In addition, patients or their caregivers have a lot of financial and temporal losses in order to ensure dietary compliance. [14] Therefore, in our study, it was aimed to evaluate the quality of life and stress levels of patients diagnosed with phenylketonuria and their parents.

Methods

This study was carried out at Hacettepe University, İhsan Doğramacı Children's Hospital, Department of Metabolism, between January 2020 and June 2020. It was planned to include patients who were followed up with the diagnosis of phenylketonuria with diet or Sapropterin hydrochloride therapy, who didn't have BH4 metabolism disorder or any other health problem. Pregnant patients were also excluded. Our aim was to evaluate the quality of life and stress levels of these patients and their families.

The research sample was formed from phenylketonuria patients followed in Hacettepe University, İhsan Doğramacı Children's Hospital, Department of Metabolism. All parents of the participants and the patients of age had given consent.Institutional ethics committee approved the study in accordance with the Declaration of Helsinki. After the participants were physically evaluated in the Department of Child Metabolism, scales to evaluate their quality of life and stress levels were applied to the participants and their parents. In our department, phenylketonuria patients are tested for phenylalanine levels every three months for routine control. The results of the blood test taken from the patients when they came for their routine control and the results of the blood tests taken at the other controls were obtained from the database.

Evaluation Tools

Rosenberg Self-Esteem Scale was developed by Morris Rosenberg in 1960. It evaluates self-esteem and consists of 10 items in total. In the Likert-type scale, which includes positively and negatively charged items, 0-1 points are considered as high self-esteem, 2-4 points as medium self-esteem, and 5-6 points as low self-esteem. [15]

State-Trait Anxiety Inventory is an inventory that measures state and trait anxiety levels of children. It has been developed by Spielberges et. al in 1983. It consists of two questionnaires with a total of 40 questions, 20 that assesses the anxiety level stately, that is, how the child feels at that moment, and 20 that assesses how he feels constantly, that is, in general. The scale is in 3-point Likert type and is evaluated with 1-3 points according to symptom severityThe lowest score that can be obtained from the scales is 20, and the highest score is 60, higher scores indicate higher anxiety. [16]

Strengths and Difficulties Questionnaire was developed by Goodman in 1997 to assess children's social, emotional and behavioral difficulties. There is a parent form for ages 4-17 and a child form for ages 11-17. It consists of 25 questions in total. [17]

Zarit Burden Scale was developed by Zarit et al. in 1980. It is a 5-point Likert-type scale consisting of 22 questions that aims to measure the distress experienced by caregivers. Answers are scored between 0-4. A minimum of 0 and a maximum of 88 points can be obtained from the scale. The high score indicates the height of the distress experienced. [18]

Parenting Stress Index aims to measure the stress experienced by parents in their relationships with their children. It is a 4-point Likert-type scale consisting of 16

questions in total. A minimum of 16 and a maximum of 64 points can be obtained from the scale. A high score from the scale indicates that parental stress is high. [19]

Statistical Analyses

Analyses were made using the IBM SPSS Statistics 23 program, a licensed product of Hacettepe University. Whether the numerical variables showed a normal distribution or not was examined using the Shapiro-Wilk test when n<50, and the Kolmogorov-Smirnov test when n>50. Number and percentage are given for qualitative variables, mean, standard deviation, median, minimum and maximum values are given for qualitative variables.Since the scale scores are in discrete numeric data type and the assumption of normality cannot be achieved, the relationships with the Spearman correlation coefficient, which is a non-parametric coefficient, were examined and the p values were examined. The significance level was 0.05, and the relationships with a p value less than 0.05 were considered statistically significant.

When the number of categories was two, if the scores in the categories were normally distributed, the "Independent Samples t Test" was performed, and the mean and standard deviations were given. For cases where the normal distribution assumption was not met, the "Mann-Whitney U Test" was performed, and medians and quartiles were given. For the variables with more than two categories, it was observed that there was no normal distribution in the categories in general, so the "Kruskal Wallis Test" was applied.In cases where the Kruskal Wallis test was applied, the "Dunn Multiple Comparison Test" was used to determine which categories were different for the results that were significant.

Results

Participants and Demographics

Data from a total of 156 phenylketonuria patients who applied to Hacettepe University İhsan Doğramacı Children's Hospital Pediatric Metabolism Outpatient Clinic between February 2020 and August 2020 were evaluated. The mean age of the 156 patients included in the study at admission was 10.9 years (±8.), and the median age was 10 (0.6-35). 53.2% of the patients were male and 46.8% were female, and the male/female ratio was 1.13 (83/73).At the time of examination, the mean age of the mothers was 37.8 years (±9), the median age was 37 (20-64), the mean age of the fathers was 40.9 years (±9.4), and the median age was 41 (17-68). Among the mothers and fathers of the patients, the rate of those with consanguineous marriage was 52.9%. The mean number of siblings was 1.23 (±1.2).
The education levels of the mothers were 2.6% illiterate, 3.3% literate, 30.1% primary school graduate, 15% secondary school graduate, 26.1% high school graduate and 22.9% university graduate. 40.5% of the mothers had a driver's license. Those with monthly income below 3000 Turkish Liras (TL) were 38.6% of the whole sample, those between 3000-6000 TL were 37.9%, those between 6000-9000 TL were 18.3%, and those over 9000 TL were 5.2%. (Table 1).

The mean age at diagnosis was 3.2 months (±10), and the median age was 0.6 months (0.07-96). 49.4% of the patients were diagnosed with classical type, 24.4%

moderate type, 26.3% mild type phenylketonuria. The mean serum phenylalanine levels of the patients at the time of diagnosis were 20.61 mg/dl (±11.82), mean serum phenylalanine levels measured when they came to the outpatient clinic examination were 7.71 mg/dl (±5.91), median serum phenylalanine levels were 7.49 mg/dl (±5.25). 85.3% of the patients who took a diet and 14.7% of those who did not. The percentage of those who adhered to the diet was 72.4% and 12.8% of those who did not. While 18.6% of the patients were receiving sapropterin dihydrochloride treatment, 81.4% were not. (Table 2)

Correlation Analysis of Patients' Scales

The scales applied to the patients were the Rosenberg self-esteem scale, the state-trait anxiety inventory, the strengths and difficulties questionnaire, and the sub-dimensions of emotional problems, behavioral problems, attention deficit and hyperactivity, peer problems, and social behaviors.

The mean score of the patients on the Rosenberg self-esteem scale was 22.19 (±5.77), and the median score was 23 (4-30). No significant correlation was found between the age of the patient and the scale scores (p=.195). A significant negative correlation was found between age at diagnosis and scale scores (r=-.27, p=.035). No significant correlation was found with serum phenylalanine level at diagnosis (p=.436), serum phenylalanine level during control examination (p=.065) and median serum phenylalanine level (p=.27). A significant and negative correlation was found with maternal age (r=-.33, p=.009) and father's age (r=-.38, p=.004). No significant relationship was found with the number of siblings (p=.352).

The mean score of the patients from the state anxiety inventory (SAI) was 29.61 (±6.93), and the median score was 29 (20-56). A significant positive correlation was found between patient age and scale scores (r=.36, p=.006). There was no significant relationship between age at diagnosis and scale scores (p=.14). No significant correlation was found with serum phenylalanine level at diagnosis (p=.11), serum phenylalanine level during control examination (p=.15) and median serum phenylalanine level (p=.25). A significant and positive correlation was found with maternal age (r=.29, p=.031) and father's age (r=.38, p=.024). No significant relationship was found with the number of siblings (p=.91).

The mean score of the patients in the trait anxiety inventory (TAI) was 33.36 (±8.51), and the median score was 32 (20-58). No significant correlation was found between patient age and scale scores (p=.062). There was no significant relationship between age at diagnosis and scale scores (p=.082). No significant correlation was found with serum phenylalanine level at the time of diagnosis (p=.18), serum phenylalanine level during the control examination (p=.27) and median serum phenylalanine level (p=.19). There was no significant relationship between maternal age (p=.36) and father's age (p=.61). No significant relationship was found with the number of siblings (p=.17).

The sub-steps and the total score of the strengths and difficulties questionnaire (SDQ) were evaluated separately. There were no significant results in terms of age and age at diagnosis. A significant and positive correlation was found between the

serum phenylalanine level at the time of diagnosis and the emotional sub-dimension of the questionnaire (r=.35, p=.036). A positive and significant correlation (r=-.34, p=.004) was found between the serum phenylalanine level in the control examination and the total score. There was no significant relationship between median serum phenylalanine levels, maternal age and number of siblings. A negative and significant relationship (r=-.34, p=.047) was found between father's age and the social sub-dimension of the questionnaire. (Table 3)

Correlation Analysis of Parents' Scales

The scales applied to the parents are the parental stress index, the Zarit burden scale, the strengths and difficulties questionnaire, and the sub-dimensions of emotional problems, behavioral problems, attention deficit and hyperactivity, peer problems and social behaviors.

The mean score from the parental stress index was 24.64 (±7.5) and the median score was 23 (8-46). No significant correlation was found between the patient's age (p=.82) and age at diagnosis (p=.23) and scale scores. No significant correlation was found with serum phenylalanine level at diagnosis (p=.094), serum phenylalanine level during control examination (p=.96) and median serum phenylalanine level (p=.52). There was no significant relationship between maternal age (p=.57) and father's age (p=.27). No significant relationship was found with the number of siblings (p=.41).

The mean score from the caregiving burden scale was 21.07 (±12.5), and the median score was 20 (0-55). No significant correlation was found between the patient's age (p=.36) and age at diagnosis (p=.57) and scale scores. No significant correlation was found with serum phenylalanine level at diagnosis (p=.055), serum phenylalanine level during control examination (p=.32) and median serum phenylalanine level (p=.1). There was no significant relationship between maternal age (p=.99) and father's age (p=.72). A positive and significant relationship (r=.195, p=.023) was found between the number of siblings and the number of siblings.

The sub-steps and the total score of the strengths and difficulties questionnaire were evaluated separately. A significant and positive correlation was found between the age of the patient and the emotional sub-dimension of the questionnaire (r=.217, p=.032). A significant and positive correlation was found between the age at diagnosis and the peer problems sub-dimension of the questionnaire (r=.211, p=.037). A significant and positive correlation was found between the serum phenylalanine level at the time of diagnosis and the behavioral sub-dimension of the questionnaire (r=.203, p=.045) and the dimension of attention deficit and hyperactivity (r=.203, p=.045). No significant correlation was found between the median serum phenylalanine levels and the phenylalanine levels in the control examination and the scales. There was no significant relationship between maternal and paternal age and the scales. No significant relationship was found with the number of siblings. (Table 4)

Comparisons Between Groups

Scale scores of patients and parents were compared according to disease type. The Kruskal Wallis test was used to determine whether there was a difference between the types in terms of scale scores, since the number of categories was more than 2 and the assumption of normal distribution was not provided. There was no significant difference between the classical type, moderate type and mild type in terms of scale scores. It was observed that there was a difference between the classical type and mild type in terms of the age of diagnosis of the patients (p=.043). The mean age at diagnosis of patients with the classical type was 85.09 months, and the patients with the mild type were 63.5 months.

When the scale scores were evaluated in terms of sapropterin intake status, a significant difference was found between the patients who received and did not receive sapropterin in terms of emotional (p=0.43), behavior (p=0.47), and social (p=0.29) sub-dimensions of the parent form of the strengths and difficulties questionnaire.

Due to the small sample size, maternal education levels were evaluated in two groups as below high school and high school and above. There was no significant difference between the two groups in any of the scales. When the groups were evaluated in terms of mother's driver's license status, a significant difference was found in the patient form of the strengths and difficulties questionnaire in terms of behavior (p=0.48) and social (p=0.25) sub-dimensions.

Scale scores were compared in terms of income level. A significant difference was found between the group with income less than 3000 TL/month and the group with 3000-6000 TL/month in terms of stateful trait anxiety inventory (p=.033). A significant difference was found between the group with an income level of 3000-6000 TL/month and the group with a 6000-9000 TL/month level in terms of the peer sub-dimension of the patient form of the strengths and difficulties questionnaire (p=.024).

Discussion

Phenylketonuria is a chronic disease, and it is a difficult disease to cope with due to the necessity of diet. Patients face many difficulties in complying with the diet, obtaining special foods, coping with the economic burden of special foods and regular controls, and adapting to social life. [13,14] Conditions such as hyperactivity, depression and anxiety, which can be observed due to the nature of the disease, also create a burden on both parents and patients. [20] The stress caused by these difficulties effects the quality of life. In this study, the difficulties and stress situations faced by patients and parents were evaluated. The results are discussed separately for both groups.

Evaluation of Patients' Outcomes

Scales indicating self-esteem, life difficulties and anxiety were used to evaluate the patient group. The Rosenberg self-esteem scale, which measures self-esteem, indicates how an individual evaluates oneself. Individuals with high self-esteem have

positive thoughts about themselves, and as a result, these individuals are self-confident and resilient in the face of difficulties. Low self-esteem leads to social introversion. In the evaluation results of our patient group's self-esteem, it was found that there was a negative correlation with the age at which the patient was diagnosed, the age of the mother and the age of the father. In a study by Iakovou et al. on the self-esteem of patients with phenylketonuria, it was shown that patients with higher dietary adherence had higher self-esteem and that self-esteem could be increased with psychiatric support. [21] In our study, in the correlation analysis of the self-esteem scale with the other scales, it was found that the state and trait anxiety inventory and the strengths and difficulties questionnaire were negatively correlated with emotional problems, behavioral problems, peer problems, hyperactivity and total scores. Decreased self-esteem indicated an increase in momentary or general anxiety and life difficulties. The effecting factor here may be that the decrease in the self-esteem of the patients may lead to a decrease in their ability to cope with difficulties. In a study by Brumm et al., it was shown that low self-esteem can be seen in children and adolescents who were treated early. [22] In our study, the patient's advanced age at diagnosis indicates low self-esteem. As the diagnosis is delayed and the uncontrolled follow-up period is prolonged, it can be concluded that the self-esteem of the patients will decrease.

The state anxiety inventory, which is used to evaluate the anxiety levels of the patients, is the scale that indicates how the patient is feeling at the moment, and the trait anxiety inventory is the scale that indicates how he/she is generally feeling, and they measure the states of tension, nervousness, fussiness and uneasiness. [16] In our study, there was no correlation between the trait anxiety scale and the variables, but a positive correlation was found between the state anxiety scale and the age of the patient, mother and father. This indicates that although the patient does not have a constant sense of anxiety, anxiety increases linearly with age at the time of admission to the outpatient clinic. In a study by Bosch et al., the most effective factor effecting the quality of life of patients with phenylketonuria was found to be emotional factors which were serum phenylalanine levels, guilt about non-compliance with diet, and serum phenylalanine levels during pregnancy. [23] Similarly, in the study of Morawska et al., it was found that the child's anxiety during blood draw and the feeling of guilt associated with diet incompatibility were the factors that effected the quality of life the most. [24] In our study, although the patients did not experience constant anxiety, their anxiety levels, which increased as age increased at the time of admission to the outpatient clinic.This may be due to the same concern about serum phenylalanine levels and guilt about non-compliance with the diet. In this study, as a result of the correlation analysis between the trait anxiety scale and other scales, the emotional, behavioral, hyperactivity and total scores of the strengths and difficulties questionnaire, negative correlation was found with social problem scores.. Especially strong correlations were found in emotional, hyperactivity and social scores. Anxiety can be expected to cause emotional and social problems. In a systematic review study by Smith and Knowles, it was shown that patients with phenylketonuria are prone to anxiety compared to healthy controls, and the disease is associated with attention deficit and hyperactivity in many studies. [25]

The strengths and difficulties questionnaire is a scale that indicates the difficulties experienced by the patient in certain areas. In our study, it was found that

as the serum phenylalanine level of the patient at the time of diagnosis increased, emotional problems increased. In a study where Jusiene et al. compared children with phenylketonuria with healthy controls, showed that patients with phenylketonuria had more emotional and behavioral problems. [26] In a study by Palermo et al., it was shown that the difficulty of maintaining the diet causes emotional problems. [27] The serum phenylalanine level at the time of diagnosis indicates the level of the patient's disease, and the higher it is, the more difficult it will be to control the disease and the more dietary phenylalanine restriction will be required. As a result, high phenylalanine levels at the time of diagnosis can be expected to cause emotional problems. In our study, in the dimension of the questionnaire related to social problem, it was found that as the age of the father increased, social problems increased. A linear relationship was found between the total score of the questionnaire and the serum phenylalanine levels in the control. This indicates the relationship between the problems such as emotional, behavioral, peer problems, and hyperactivity that patients encounter in life with serum phenylalanine levels. Similarly, in the study of Morawska et al., phenylketonuria symptoms and social impact have been found to be associated with emotional and behavioral difficulties. [24]

There are various opinions in studies about the effect of sapropterin use on quality of life. Considering that it reduces the need for restriction of phenylalanine in the diet, it can be thought that the use of sapropterin will increase the quality of life.However, in most of the studies conducted in the literature, no significant difference was found in terms of quality of life between users and non-users. [28,29] When the patients were evaluated in terms of sapropterin use in our study, a significant difference was found between the patients who used and did not use in the emotional problems, behavioral problems and social problems sub-dimensions of the strengths and difficulties questionnaire. Similarly, in the study of Cazzorla et al. [30], a significant difference was found in the quality of life of patients with mild phenylketonuria who were treated with sapropterin and those with classical phenylketonuria who were followed up with diet therapy. However, in this study, it was thought that this difference in the mild group might be due to the lesser severity of the disease.

Evaluation of Parents' Outcomes

Factors that determine the low quality of life of the parents of phenylketonuria patients have been reported to be high stress levels, depression or anxiety in the family, lack of social support, loss of friends, and a young age of the patient. [24] Parental stress index, Zarit burden scale and strengths and difficulties questionnaire were applied to parents in our study. Parental stress index could not be associated with other variables in our parent group. On the other hand, a linear relationship was found between the Zarit burden scale and the number of siblings. It was observed that the burden of caregiving increased as the number of children in the family increased. In a study conducted in our country to evaluate the life difficulties of patients with phenylketonuria, it was observed that families were reluctant to have children again.[31] In a study conducted in our clinic, it was observed that families had difficulties in terms of diet between healthy siblings and children with phenylketonuria. [32] In a study by Alaei et al., average phenylalanine levels and some factors affecting social status were compared. No relationship was found in terms of family size. [33] In our study, there were no corelation in the increase in the number of sibling, the median serum phenylalanine levels of the patients and the parental stress index. From this, it

can be concluded that the size of the family does not cause any disruption in the follow-up of the patients, but creates difficulties in the life of the family.

Due to the nature of the phenylketonuria disease, attention deficit and behavioral problems can be seen in patients with a diagnosis of phenylketonuria. [20] In the study of Ford et al., it was also shown that children with phenylketonuria experience social exclusion and relationship problems. [20] In our study, a linear relationship was found between the behavioral problems, attention deficit and hyperactivity sub-dimensions of the strengths and difficulties questionnaire and the phenylalanine level at the time of diagnosis. Similarly, it was observed that peer problems increased with the advanced age at diagnosis. High serum phenylalanine levels at the time of diagnosis are associated with clinically severe disease or late diagnosis. For this reason, it can be assumed that patients will have behavioral and attentional problems in case of more severe disease state or late diagnosis, and also peer problems in case of late diagnosis.

There are studies conducted to evaluate the effect of social status in phenylketonuria. Alaei et al. showed the relationship between social status and dietary compliance. A linear relationship was found between the education level, marital and working status of the parents and the median phenylalanine levels. [33] Cotugno et al. [34] found that phenylalanine intake increased as maternal education level decreased, in the study performed in our clinic, Özel et al. showed that the knowledge level of the mother and the median serum phenylalanine level were inversely proportional.[35] Mahmoudi et al. reported in a study that one of the factors most associated with caregivers' quality of life was caregiver's work. [36] In this study, the mother's education level, whether the mother has a driver's license and monthly income were used as indicators of social status. No significant difference was found regarding any variable related to the education level of the mother. However, it was observed that there was a significant difference between behavioral problems and social problems of the strengths and difficulties questionnaire in terms of the presence or absence of the mother's driver's license. In comparisons made in terms of income level, it was seen that there was a significant difference between income levels in terms of peer problems of the state anxiety scale and the strengths and difficulties questionnaire.

When the relationship between the scales was examined in our study, it was seen that the Zarit burden scale was correlated with all sub-dimensions of the parent form of the strengths and difficulties questionnaire and with the parent stress scale. There was also a correlation with all parts of the strengths and difficulties questionnaire, except for the peer problems part of the patient form. This indicates that the increase in the life difficulties of patients and parents increases the burden of caregiving. It can be said that the increase in the burden of caregiving also increases the parental stress levels. Finding solutions for emotional, behavioral, social problems, peer problems and hyperactivity problems that children face in life will reduce the stress levels of families. A systematic review by Edelstein et al. also supports this.[37] He reported that stress can be reduced through appropriate support in caregivers of children with chronic diseases and that the burden of caregiving can be reduced with various interventions. Some recent studies have also indicated the hardships of livinhg with phenylketonuria. A meta-analysis made in Latin American patients showed that the disease brought high burden with it. [38] A systematic review by Thomas et al. in Phenlketonuria patients' caregivers concluded that they had poor to moderate health related quality of life. [39]

Phenylketonuria is one of the most difficult diseases to cope with. It is known that behavioral problems of patients increase as a result of uncontrolled disease. In this study, it was observed that self-esteem decreased especially in the case of late diagnosis. As a result, patients encounter emotional and social problems and difficulties in relationships with peers. Especially in patients with late diagnosis and poor diet control, providing psychological support even if there is no clinical sign of psychiatric disease will increase the patient's self-esteem and make it easier to cope with difficultiesThis is a situation that will facilitate the control of the disease. In our study, we also observed that the anxiety of coming to the outpatient clinic increases as the age of the patients increases, that is, the longer the follow-up period. There may be multiple reasons for this, questioning this in the outpatient clinic examinations on an individual patient basis. It will be useful to offer solutions for the patient's concerns about the outpatient clinic application. One of our findings was that as the age of the father increased, the patients' self-esteem decreased and their social problems increased. The vast majority of patients apply to our clinic accompanied by their mothers for a control examination. Including fathers in the follow-up and treatment process, questioning their knowledge about the disease,ensuring the patient's participation in the follow-up process can make an important contribution. Another finding we found was that the burden of caregiving for families increased as the number of children increased. As pediatricians, problems related to healthy siblings, as well as siblings with phenylketonuria, are also included in the field of pediatrics. It may be appropriate to question the attitudes of the family towards their children and to evaluate the attitudes and perceptions of healthy siblings about the disease. As with every disease, phenylketonuria is a disease that requires a holistic approach. In this disease, it would be appropriate to question the home and family environment in order to provide good disease control and to increase the quality of life of the patients and their parents. More individualized studies on the subject are needed.

References

1. National Center for Biotechnology Information. PubChem Compound Summary for CID 6140, Phenylalanine. Available from: https://pubchem.ncbi.nlm.nih.gov/compound/Phenylalanine. Accessed Apr. 10, 2020
2. Blau N, van Spronsen FJ, Levy HL. Phenylketonuria. *Lancet* 2010; 376(9750):1417-27
3. Camp KM, Parisi MA, Acosta PB, Berry GT, Bilder DA, Blau N, et al. Phenylketonuria Scientific Review Conference: state of the science and future research needs. *Mol Genet Metab.* 2014;112(2):87-122
4. Scriver, C. R**.** The PAH gene, phenylketonuria, and a paradigm shift**.** *Hum. Mutat.* 2007; 28: 831-845
5. Zeybek C. Phenylketonuria Screening Program. I.U. Cerrahpasa Faculty of Medicine Continuing Medical Education Activities 2003;35, 65-71
6. Loeber JG. Neonatal screening in Europe; the situation in 2004. *J Inherit Metab Dis.* 2007;30(4):430-8
7. National institutes of health consensus development panel. National institutes of health consensus development conference statement: phenylketonuria: screening and management, October 16–18, 2000. Pediatrics 2001; 108: 972–82

8. Guldberg P, Henriksen KF, Sipila I, Guttler F, de la Chapelle A. Phenylketonuria in a low incidence population: molecular characterisation of mutations in Finland. *J Med Genet* 1995; 32: 976–78
9. Smith I, Lee P. The hyperphenylalaninemias. J . Fernandes, J.M. Saudubray, G. Van Den Berghe ,editors Inborn Metabolic Diseases: Diagnosis and Treatment. 2nd ed. New York: Springer-Verlag Berlin Heidelberg, 2000
10. Campeau PM, Bernard G, Clayton PT. Neurotransmitter diseases and related conditions. *Mol Genet Metab.* 2007 ;92(3):189-97
11. van Wegberg, A., MacDonald, A., Ahring, K., Bélanger-Quintana, A., Blau, N., Bosch, A. ve ark. The complete European guidelines on phenylketonuria: diagnosis and treatment. Orphanet journal of rare diseases, van Wegberg AMJ, MacDonald A, Ahring K, et al. The complete European guidelines on phenylketonuria: diagnosis and treatment. *Orphanet J Rare Dis.* 2017;12(1):162
12. Coskun T. Hyperphenylalaninemias. Murat Yurdakök, editor Yurdakök Pediatri, Ankara: Güneş Tıp Kitabevleri, 2017
13. Ustuner Top F, Kucukalemdar D. The Difficulties of Children with Phenylketonuira: A Qualitative Study. *Head.*2015;12(1):62-68
14. Rose, A. M., Grosse, S. D., Garcia, S. P., Bach, J., Kleyn, M., Simon, N. E., Prosser, L. A. . The financial and time burden associated with phenylketonuria treatment in the United States. *Mol Genet Metab Rep.* 2019;21:100523
15. Çuhadaroğlu F. Self-Esteem in Adolescents. [Master thesis]. Ankara: Hacettepe University Faculty of Medicine; 1986
16. Özusta, Ş. Adaptation, validity and reliability study of the state-trait anxiety inventory for children [Master's thesis]. Ankara: Hacettepe University Institute of Social Sciences; 1993
17. Güvenir, T., Özbek, A., Baykara, B., Arkar, H., Şentürk, B., İncekaş, S. Psychometric properties of the Turkish adaptation of the Strengths and Difficulties Questionnaire (SGA). *Journal of Child and Youth Mental Health,* 2008; 15(2), 65-74
18. İnci F.H. , Erdem M. Translating the Zarit Burden Scale into Turkish Adaptation Validity and Reliability. *Ataturk University Nursing Vocational School Journal,* 2008;11(4): 85-95
19. Özmen-Kaymak, S., ve Özmen, A. Development of the Parenting Stress Index. *National Education Journal,* 2012; 42(196), 20-35
20. Ford S, O'Driscoll M, MacDonald A. Living with Phenylketonuria: Lessons from the PKU community. *Mol Genet Metab Rep.* 2018;17:57-63
21. Iakovou, K., Schulpis, K. Self-estimation of phenylketonuria patients on therapeutic diet. *Psychological support. Drug Metab Pers Ther.* 2020;35(2)
22. Brumm VL, Bilder D, Waisbren SE. Psychiatric symptoms and disorders in phenylketonuria. *Mol Genet Metab.* 2010;99 Suppl 1:S59-63
23. Bosch AM, Burlina A, Cunningham A, Bettiol E, Moreau-Stucker F, Koledova E, et al. Assessment of the impact of phenylketonuria and its treatment on quality of life of patients and parents from seven European countries. *Orphanet J Rare Dis.* 2015 (18);10:80
24. Morawska A, Mitchell AE, Etel E, Kirby G, McGill J, Coman De et al. Psychosocial functioning in children with phenylketonuria: Relationships between quality of life and parenting indicators. *Child Care Health Dev.* 2020;46(1):56-65.

25. Smith I, Knowles J. Behaviour in early treated phenylketonuria: a systematic review. *Eur J Pediatr.* 2000 Oct;159 Suppl 2:S89-93
26. Jusiene R, Kucinskas V. Familial variables as predictors of psychological maladjustment in Lithuanian children with phenylketonuria. *Med Sci Monit.* 2004;10(3)
27. Palermo L, MacDonald A, Limback E, Robertson L, Howe S, Geberhiwot T, et al. Emotional health in early-treated adults with phenylketonuria (PKU): Relationship with cognitive abilities and blood phenylalanine. *J Clin Exp Neuropsychol.* 2020;42(2):142-159
28. Feldmann R, Wolfgart E, Weglage J, Rutsch F. Sapropterin treatment does not enhance the health-related quality of life of patients with phenylketonuria and their parents. *Acta Paediatr.* 2017;106(6):953-959
29. Demirdas S, Maurice-Stam H, Boelen CC, Hofstede FC, Janssen MC, Langendonk JG, et al. Evaluation of quality of life in PKU before and after introducing tetrahydrobiopterin (BH4); a prospective multi-center cohort study. *Mol Genet Metab.* 2013;110 Suppl:S49-S56
30. Cazzorla C, Cegolon L, Burlina AP, et al. Quality of Life (QoL) assessment in a cohort of patients with phenylketonuria. BMC Public Health. 2014;14:1243
31. Bilginsoy C, Waitzman N, Leonard CO, Ernst SL. Living with phenylketonuria: perspectives of patients and their families. *J Inherit Metab Dis.* 2005;28(5):639-649
32. Zengin Akkus P, Bilginer Gurbuz B, Ciki K, Ilter Bahadur E, Karahan S, Ozmert EN et al. Caring for a Child with Phenylketonuria: Parental Experiences from a Eurasian Country. *J Dev Behav Pediatr.* 2020;41(3):195-202
33. Alaei M, Asadzadeh-Totonchi G, Gachkar L, Farivar S. Family social status and dietary adherence of patients with phenylketonuria. Iran *J Pediatr.* 2011;21(3):379-384
34. Cotugno G, Nicolò R, Cappelletti S, Goffredo BM, Dionisi Vici C, Di Ciommo V. Adherence to diet and quality of life in patients with phenylketonuria. *Acta Paediatr.* 2011;100(8):1144-1149
35. Özel HG, Kucukkasap T, Koksal G, Sivri HS, Dursun A, Tokatli A, Coskun T. Does maternal knowledge impact blood phenylalanine concentration in Turkish children with phenylketonuria? *J Inherit Metab Dis.* 2008;31 Suppl 2:S213-7
36. Mahmoudi-Gharaei J, Mostafavi S, Alirezaei N. Quality of Life and the Associated Psychological Factors in Caregivers of Children with PKU. *Iran J Psychiatry.* 2011;6(2):66-69
37. Edelstein H, Schippke J, Sheffe S, Kingsnorth S. Children with medical complexity: a scoping review of interventions to support caregiver stress. *Child Care Health Dev.* 2017;43(3):323-333
38. Pessoa ALS, Martins AM, Ribeiro EM, Specaola N, Chiesa A, Vilela D et al. Burden of phenylketonuria in Latin American patients: a systematic review and meta-analysis of observational studies. *Orphanet J Rare Dis.* 2022;17(1):302.
39. Shaji Thomas D, K Y D, Arulappan J. Health Related Quality of Life of Caregivers of Children and Adolescents With Phenylketonuria: A Systematic Review. *Glob Pediatr Health.* 2021;8:2333794X211065333.

Table 1. Demographic characteristics of the patients included in the study

Feature	n (%)
Number of patients	156
Gender (Girl/Boy)	73 (46.8) /83 (53.2)
Age (years)	
Mean ± SD	10.9±8.8
median (range)	10 (0.6-35)
Maternal age (years)	
Mean ± SD	37.8±9
median (range)	37 (20-64)
Father age (years)	
Mean ± SD	40.9±9.4
median (range)	41 (17-68)
Number of siblings	
Mean ± SD	1.23±1.2
median (range)	1 (0-7)
Kinship between parents	
There is	81 (52.9)
no	72 (47.1)
Mother's education level	
Illiterate	4 (2.6)
Literate	5 (3.3)
Primary education	46 (30.1)
secondary education	23 (15)
High school	40 (26.1)
University	35 (22.9)
mother's license	
There is	62 (40.5)
no	91 (59.5)
Income level (monthly)	
less than 3000 TL	59 (38.6)
3000-6000 TL	58 (37.9)
6000-9000 TL	28 (18.3)
more than 6000 TL	8 (5.2)

Table 2. Disease characteristics of the patients included in the study

Feature	n (%)
Age at diagnosis (months)	
Mean ± SD	3.2±10
median (range)	0.6 (0.07-96)
Disease type	
Classical	77 (49.4)
moderate	38 (24.4)
Mild	41 (26.3)
Serum phenylalanine level at diagnosis (mg/dl)	
Mean ± SD	20.61 (±11.82)
median (range)	18.16 (4.03-59.48)
Serum phenylalanine level (mg/dl) in the control examination	
Mean ± SD	7.71 (±5.91)
median (range)	6.3 (0.4-27.73)
Median serum phenylalanine level (mg/dl)	
Mean ± SD	7.49 (±5.25)
median (range)	5.94 (37.9)
Diet status	
There is	133 (85.3)
no	23 (14.7)
status of adherence to diet	
There is	113 (72.4)
no	20 (12.8)
Not dieting	23 (14.7)
Sapropterin dihydrochloride intake status	
There is	29 (18.6)
no	127 (81.4)

Table 3. Correlation analysis results of patients

	Rosenberg	TAI	SAI	SDQ emotion	SDQ behavior	SDQ ADHD	SDQ peer	SDQ social	SDQ total
Age	-.165	**.358***	0.67	-.105	.150	-.055	-.004	-.269	-.008
Age at diagnosis	**-.266***	.195	.231	.097	.193	-.055	.148	-.235	.115
Phe level at diagnosis	-.100	.214	.179	**.351***	.230	.243	-.208	-.018	.215
Median Phe levels	-.141	.154	.176	.200	.074	.063	.116	.125	.166
Phe levels at control	-.234	.191	.146	.281	.233	.178	.211	-.094	**.338***
Age of mother	**-.329***	**.289***	.068	.015	.225	-.007	-.007	-.243	.034
Age of father	**-.287***	**.376***	.123	.115	.185	.102	.192	**-.338***	.157
Number of siblings	-.120	-.015	.182	.022	-.037	-.152	.326	-.038	.019

Phe: Phenylalanine ,TAI: Trait Anxiety Inventory, SAI: Stait Anxiety Inventory, SDQ: Strengths and Difficulties Questionnaire, ADHD: Attention Deficit and Hyperactivity Disorder
**p <0.05*

Table 4. Parents' correlation analysis results

	Parental Stress Scale	Zarit Burden Scale	SDQ emotion	SDQ behavior	SDQ ADHD	SDQ peer	SDQ social	SDQ total
Age	.077	.19	**.217***	-.005	-.024	.035	.024	.087
Age at diagnosis	.101	.049	.177	.182	.042	**.211***	-.056	.187
Phe level at diagnosis	.163	.142	.146	**.203***	**.203***	-.080	-.101	.173
Median Phe levels	.137	.055	.192	.068	.060	.008	.026	.110
Phe levels at control	.084	.004	.185	.156	.059	.081	-.094	-.076
Age of mother	.048	-.001	.038	-.26	-.102	-.090	.119	-.063
Age of father	.094	.030	.126	.059	.088	-.135	.164	-.034
Number of siblings	.070	**.195***	.071	-.050	-.132	-.074	-.020	-.022

SDQ: Strengths and Difficulties Questionnaire
**p <0.05*