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Investigation of Eating Behaviors and Dietary Compliance of Adult Individuals with Phenylketonuria

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ABSTRACT

Phenylketonuria (PKU) is a congenital metabolic disorder caused by a deficiency of phenylalanine hydroxylase. Left untreated, it can lead to severe neurological damage. Early diagnosis is possible thanks to newborn screening programs, and effective treatment includes a low-protein diet, medical nutritional supplements and regular monitoring of phenylalanine (Phe) levels in the blood. The prevalence of PKU in Turkey is high, occurring in every 3,500-4,000 live births. Compliance with the diet may be difficult due to various individual and environmental factors. Social pressures, busy daily life, problems in accessing high-cost special diet products and lack of information about phenylalanine content are the main barriers that negatively affect adherence. In addition, the stress of dietary control of the disease and the feeling of stuck eating lead to impaired eating behaviors and increased risk of eating disorders. This relationship is supported by the observation that eating disorders are more common in individuals with low metabolic control. Although this relationship is accepted in the European PKU guidelines, more research is needed due to the lack of literature. Supporting dietary compliance and directing individuals with impaired eating behavior to healthy eating habits are of great importance in terms of treatment efficacy and quality of life. Therefore, multidisciplinary and comprehensive support mechanisms should be developed.

1. INTRODUCTION

Phenylketonuria (PKU) is an autosomal recessive congenital metabolic disorder in which phenylalanine metabolism is impaired due to phenylalanine hydroxylase deficiency [1]. Due to deficiency in phenylalanine hydroxylase (PAH) enzyme or BH4 cofactor deficiency, phenylalanine (Phe) cannot be metabolized and its level in the blood increases [2]. Increased Phe level may cause toxic effects in the brain and lead to cognitive retardation, seizures and behavioral problems [3].

Currently, the most effective approach in the treatment of PKU is a lifelong low-protein diet with medical foods to meet the daily protein requirement and regular monitoring of Phe levels. However, the fact that nutrition is under constant medical supervision may negatively affect individuals' eating behaviors and body perception; this may lead to the development of unhealthy attitudes [4]. The risk of eating disorders increases in chronic diseases requiring lifelong diet. This risk is thought to be high in individuals with PKU and it is known that dietary compliance decreases significantly especially in adolescence and adulthood [5].

PKU dietary cessation in childhood can lead to permanent cognitive and emotional problems such as mental retardation, learning disabilities and anxiety, and personality disorders in adolescence and young adulthood [6]. Early diagnosis and a Phe-restricted diet can largely prevent the neurodevelopmental effects of the disease. However, PKU is still under investigation and alternative treatment methods to diet are being developed [7]. Decreased adherence impairs metabolic control and increases long-term cognitive risks [8]. In addition, poor metabolic control increases the likelihood of disordered eating behavior and eating disorders [2].

In this context, examining the causes of dietary compliance difficulties in adults with PKU, evaluating eating behaviors and identifying

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possible risk factors in line with the existing literature is important in terms of both increasing treatment effectiveness and improving quality of life. The aim of this review study is to systematically summarize the existing knowledge in the field, to reveal the remarkable gaps in the literature and to provide a scientific basis for future research. It is aimed that the findings obtained will contribute to the development of holistic support approaches to improve the quality of life of individuals with PKU.

2.PHENYLKETONURIA: HISTORY, EPIDEMIOLGY AND CLASSIFICATION

PKU was first described by Norwegian physician Asbjørn Følling in 1934. Følling detected phenylpyruvic acid accumulation in the urine of two brothers with mental retardation and named this condition as "imbecillitas phenylpyrouvica", and in the following years, this disease was named "phenylketonuria"[9]. An important step was taken in the management of the disease with the Phe-restricted diet therapy developed by Dr. Horst Bickel in the 1950s. The efficacy of this treatment approach was proven by clinical observations [10,11]. In a study published in 1958, Woolf et al. emphasized the importance of early diagnosis and stated that the disease could be detected with a simple urine test [12,13]. With the "Guthrie test" developed by Dr. Robert Guthrie in the 1960s, early diagnosis of PKU became possible in newborn screening [14].

The prevalence of PKU varies considerably depending on geographical and genetic factors. The average prevalence across Europe is around 1:10,000. However, this rate varies by country; it has been reported as 1:2,700 in Italy, 1:4,500 in Ireland and 1:100,000 in Finland. Rates are more variable in Asia and the Middle East. In Iran, rates as high as 1:5,000 are observed, while in Japan they are as low as 1:120,000. These differences are thought to be due to genetic structure and health policies [15,16]. The prevalence of PKU in Turkey is approximately 1:3,500-4,000, which is above the world average. An average of 300 children are born with PKU each year and the carrier rate in the community is around 4% [17]. The high prevalence in Turkey is directly related to the prevalence of consanguineous marriages. Studies show that the rate of consanguinity among the parents of PKU patients is as high as 65% [18].

The disease is phenotypically classified according to Phe levels in the blood. According to the classification made in 1980, individuals with Phe levels above 1200 µmol/L were defined as classical PKU, between 600-1200 µmol/L as variant PKU, and individuals below 600 µmol/L as mild hyperphenylalaninemia (HPA) [19]. In more recent classifications:

- 120-600 µmol/L: Mild HPA,
- 600-900 µmol/L: Mild PKU
- 900-1200 µmol/L: Moderate PKU,
- 1200 µmol/L: Defined as classic PKU [20].

In evaluations based on daily dietary Phe tolerance, individuals with a tolerance of less than 250 mg/day are classified as classic PKU and those with a tolerance of 250-400 mg/day are classified as mild/moderate PKU [3].

These classifications play a critical role in both diagnosis and treatment planning. Early diagnosis and appropriate treatment significantly improve the quality of life of patients and prevent severe neurologic damage.

3. DIAGNOSTIC PROCESS AND TREATMENT APPROACHES IN PKU

Newborn screenings are preventive health services that aim to reduce mortality and morbidity by identifying diseases that can be treated with early diagnosis before they become symptomatic [21]. These screenings were first initiated in the 1960s to detect PKU and have since become widespread successfully and have assumed an important role in the early diagnosis of many metabolic diseases [22]. The heel prick test is a simple screening method for the early detection of metabolic diseases in newborn infants. Blood taken from the heel of the baby is dripped onto a special filter paper and sent to the laboratory. In the most common method, the Guthrie test, high levels of phenylalanine in the blood stimulate the growth of Bacillus subtilis bacteria and a halo forms around the blood drop. This halo is evaluated by comparing it to samples with known phenylalanine levels. The test can detect diseases such as PKU at an early stage [23].

In Turkey, PKU screening was initiated as a pilot project in 1983 and the results showed that the prevalence of PKU was higher than expected [24]. The program, which was officially initiated by the Ministry of Health in 1986, was implemented nationwide in 1994. While the screening prevalence was 4.7% in 1987, it reached 86.3% in 2006 and 95% in 2008 [25]. Today, in addition to PKU, many other diseases such as congenital hypothyroidism, biotinidase deficiency and spinal muscular atrophy are included in the scope of screening. Thanks to these programs, approximately 4500 babies are protected from permanent damage due to various metabolic and genetic diseases every year [26].

The main approach in the treatment of individuals diagnosed with PKU is a multidisciplinary follow-up process with a special

diet to reduce Phe levels. Phe-restricted diet includes limiting natural protein sources (meat, milk, eggs, legumes) and meeting the protein requirement with Phe-free medical nutrition products. Carbohydrates and fats play an important role in meeting energy needs [27]. The need for treatment is determined by blood Phe levels. Below 360 µmol/L, no treatment is required, while treatment is recommended for levels between 360-600 µmol/L until 12 years of age. Levels above 600 µmol/L require lifelong treatment. It is recommended to maintain Phe levels below 360 µmol/L in women planning pregnancy and in maternal PKU cases [28]. According to the American College of Medical Genetics and Genomics (ACMG) guidelines, lifelong treatment is recommended in individuals with PAH deficiency and Phe levels above 360 µmol/L. Keeping this level under control before and during pregnancy is important for the health of both mother and baby [29].

In addition to dietary therapy, sapropterin (BH4) treatment may improve Phe tolerance in patients who respond to this drug. There are also enzyme therapies used in the US and approved in Europe; however, these methods have limited application due to serious side effects. Currently, studies on innovative approaches such as gene therapy are ongoing [6].

4. COMPLIANCE PROBLEMS AND FACTORS AFFECTING DIETARY ADHERENCE IN PKU

The main approach in the treatment of PKU has been dietary restriction of Phe intake for the last sixty years. Although this form of treatment is generally effective, it is known that patients face various difficulties in adhering to this diet in the long term [30]. Adherence to dietary treatment may make its sustainability difficult due to individual and environmental factors. In particular, factors such as pressure from the social environment, temporal constraints, the cost of special diet products, and the individual's living independently from the family are the main reasons that negatively affect adherence. In addition, individuals' lack of adequate knowledge about Phe content, inadequacy of appropriate products, and lack of awareness of the effects of diet on disease are also considered as reasons that make sustainability difficult [31]. In the study conducted by Tandoğan and Bilgin in Turkey, it was reported that families experienced various difficulties in the dietary adaptation process. These difficulties include inaccessibility of dietary products, difficulty in accessing a dietitian, high cost of products, costly transportation to the hospital, and difficulty in adapting to the diet in social environments [32].

Many factors affecting adherence to dietary therapy are similar to those previously identified for inherited metabolic diseases. McDonald categorized these factors into three main groups: difficulties with amino acid supplements (e.g., unpleasant taste and difficulty in use), the social and psychological burden of dieting (e.g., social isolation, difficulty at work, embarrassment), and additional factors such as patient responsibility, family characteristics, lack of information, and perception of the impact of dieting [33]. A study on the challenges faced by people with PKU when eating out assessed the experiences of people with PKU and their caregivers through an online survey conducted in the UK. Most respondents cited the limited choice of low-protein meals and lack of information about the protein content of foods as the biggest barriers to dietary adherence [34].

A study of adult PKU patients in Italy found that dietary adherence was generally low. Most participants consumed too much natural protein and did not use amino acid supplements as often as recommended. The most frequently cited reason for nonadherence was social pressure (55%), while taste and difficulty in using the products were also influential. In contrast, regular Phe measurement (61%) and metabolic center monitoring (49%) were cited as factors that increased adherence [35].

In a recent study of 30 adult patients with PKU, marked differences in adherence to a Phe-restricted diet were observed. Sixteen patients adhered to the diet and maintained a low Phe intake, while 14 did not adhere to the diet for an average of 5.4 years. Blood Phe concentrations remained within the recommended range (120-600 µmol/L) in patients who adhered to the diet, whereas these values were significantly higher in those who did not [36]. Weekly individual dietitian meetings have emerged as one of the most effective strategies to improve adherence in PKU treatment. These meetings facilitate diet sustainability by supporting motivation. It also contributes to the improvement of metabolic control and significantly increases treatment adherence [37]. Children with PKU need to strictly adhere to a low-protein diet to effectively manage their condition. Pinto et al. examined blood Phe levels in PKU patients in Europe and Turkey, highlighting that these levels generally worsen with age and the need for continuous monitoring and management [38].

At the consensus conference, experts noted that the sustainability of medical nutrition therapy becomes difficult, especially from early adolescence onwards, and that this hinders strict adherence to a Phe-restricted diet for most patients. It is also widely accepted that this treatment has limited capacity to effectively control blood Phe

concentrations in the long term [39]. On the other hand, adherence to the PKU diet is significantly influenced by factors such as social support, positive treatment attitudes and access to specialty foods. Early initiation of a Phe-restricted diet favorably supports cognitive development in children with PKU. However, dietary adherence generally decreases after adolescence. Although lifelong treatment is recommended, dietary adherence is often inadequate, which can lead to nutritional deficiencies and various health problems [40]. One clinical study found that many adult PKU patients were not receiving treatment despite being at risk of brain dysfunction. 152 active patients and 162 previously treated patients were analyzed, 47 could not be reached, 63 of 115 patients were informed and 21 returned to treatment. The main factors preventing return to treatment included lack of insurance, lack of understanding of the importance of the disease and psychosocial problems [41].

In recent years, there have been suggestions in the literature that PKU should be considered not only as a metabolic disorder but also as a "compliance disease" requiring continuous adherence to treatment [42]. Indeed, a study conducted in the UK showed that non-compliance with Phe restriction and inadequate consumption of low-Phe protein products were associated with low micronutrient levels and poor metabolic control in adult PKU patients who could not maintain their diet. These data are consistent with studies conducted in different geographies and underline similar metabolic risks globally [36].

5. PKU AND EATING BEHAVIOR: PSYCHOSOCIAL DIMENSION

An eating disorder refers to abnormal eating behaviors that do not fit a specific diagnosis and can manifest as restrictive eating, emotional eating or uncontrolled eating. These behaviors can be triggered by external factors such as socioeconomic status, familial influences and social experiences [43]. Disordered eating and eating disorders are seen in adults with PKU; disordered eating is of lower severity and intensity than eating disorders, but both can affect daily life [44,48]. In one study, the eating attitudes and behaviors of 15 individuals with PKU aged 12-35 years were examined; it was found that individuals with poor metabolic control showed eating disorder symptoms more frequently than those with good control. Although the number of participants was limited, the results suggest that individuals with PKU may be at increased risk for disordered eating behaviors [4].

In another study conducted in the UK, individuals with PKU reported that the biggest problems when eating out were the lack of low-protein options and lack of information. Most participants were dissatisfied with their experience, while special dietary requests were frequently not met. The findings suggest that eating out may increase the risk of eating disorders by making dietary adherence difficult [34].

Eating disorders are associated not only with eating behavior but also with self-perception and trauma. In individuals with PKU, strict diet therapy disrupts eating behavior and increases emotional burden, especially in adolescence, conflicting with body perception and self-worth, increasing the risk of eating disorders. Social pressures and difficulties in treatment compliance may turn eating behavior into a means of control. Therefore, eating disorders in individuals with PKU have a metabolic and psychosocial dimension [45]. According to the study, the mean BMI of adult PKU patients ranged between 26-30.3 kg/m^2, and obesity rates were 2-3 times higher than in the control group, especially in women. This was associated with eating disorders, diet, psychosocial factors and lifestyle and the study emphasizes the importance of weight control and healthy nutrition [46]. The prevalence of eating disorders in the PKU patient population is significantly higher than in the general population. Compliance with dietary therapy is influenced by various psychological and social factors. This can have significant effects on the overall health status of PKU patients [34].

A study conducted with adults with PKU found that the prevalence of eating disorders was significantly higher compared to the general population. The prevalence of eating disorders in individuals with PKU was reported as 3.4%, while it was 1.9% in individuals with diabetes and 0.9% in the general population. These findings suggest that adults with PKU are approximately four times more likely to develop an eating disorder than the general population [45]. In another study conducted with women with type 1 diabetes and PKU, eating attitudes and psychological adjustment were assessed with questionnaires. Although symptoms of disordered eating were similar, behavior patterns differed. The findings suggest that diet-managed chronic diseases may increase the risk of eating disorders. The findings reveal that eating disorders are not only a statistical but also a clinically important problem for individuals with PKU, emphasizing the need for mental health support in PKU management [5].

At the consensus conference, experts agreed that in PKU patients on a low-phenylalanine diet, the restrictive nature of the diet, limited food choice

and a constant focus on dieting may increase the risk of eating disorders, especially in individuals with low Phe tolerance [39]. It was emphasized that more research is needed in this area in the future. While the European Guidelines on PKU recognize the existence of eating disorders, the lack of literature and the absence of PKU-specific eating disorder questionnaires suggests that more research is needed in this area [1,47].

2. Conclusion

PKU is an inherited metabolic disorder that can lead to severe neurological damage and cognitive decline if left untreated. However, with early diagnosis and effective treatment, these risks can be largely prevented and individuals can lead almost normal lives. Phe-restricted diet therapy plays a key role in this success. The earlier treatment is initiated and the better adherence is achieved, the more favorable the neurocognitive outcomes.

The high prevalence of PKU in Turkey compared to the world average necessitates raising public awareness of this disease. Ensuring the sustainability of treatment adherence requires the cooperation of not only the individual but also the family, health professionals and the social environment.

Difficulties experienced in maintaining diet treatment directly reduce the effect of the treatment and negatively affect the individual's quality of life. At this point, eating behaviors in particular become an important determinant of compliance with treatment. Strict dietary restrictions can cause behavioral patterns in individuals that can lead to food-related anxiety, suppressing the desire to eat, avoiding social environments, and even eating disorders. During adolescence and young adulthood, the feeling of not being able to consume the same foods as their peers can lead to emotional disruptions in eating behaviors and deviations from the diet. In addition, dulling of the sense of taste with limited taste alternatives may cause individuals to move away from diet products over time. Therefore, it is very important to recognize individuals with problems in eating behaviors at an early stage and to support these individuals with both nutritionists and psychological counseling teams. Personalized nutrition programs, diversification of dietary products and the provision of trainings that give meaning to the individual's diet can provide more successful management of this process. In future studies, a special screening tool that takes into account disease-specific characteristics can be developed to distinguish between treatment-related eating behaviors and pathological eating disorders in diseases requiring chronic diet such as PKU.

In conclusion, PKU management cannot be sustained by individual efforts alone; it requires a multi-stakeholder, interdisciplinary and long-term approach. A holistic support system in which individuals, families and health professionals actively participate should be developed to increase treatment adherence and sustain quality of life. In this context, the formation and coordinated work of multidisciplinary teams consisting of nutritionists, psychological counselors, social workers and physicians should be supported. Furthermore, integration of national health policies and clinical practices is of great importance for the effective management of PKU. In particular, concrete steps such as including low-protein medical foods within the scope of health insurance, including psychological support protocols in the treatment process and expanding guidance services for families will be effective in improving both treatment adherence and quality of life. Thus, the burden of disease on the lives of individuals with PKU can be minimized and their full participation in society can be supported.

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Conflict of Interest

No conflict of interest is declared by the authors. In addition, no financial support was received.

Author Contributions

Study Design: ABD, ASK; Data Collection: ABD, ASK; Statistical Analysis: ABD; Data Interpretation: ABD, ASK; Manuscript Preparation: ABD, ASK; Literature Search: ABD, ASK. All authors have read and agreed to the published version of the manuscript.

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