The Turkish Journal of Pediatrics 2021; 63: 790-800
https://doi.org/10.24953/turkjped.2021.05.007

Original Article

COVID-19-related anxiety in phenylketonuria patients

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ABSTRACT

Background. Phenylketonuria (PKU) is an inherited disorder of amino acid metabolism, the treatment of which often requires a special diet to prevent adverse neuropsychiatric outcomes. In the COVID-19 pandemic, which has had a substantial effect on the whole world since the beginning of 2020, PKU patients represent a vulnerable population because they may be dependent on special nutritional products, have limited access to routine care and display increased levels of anxiety.

Methods. For this reason, an online questionnaire assessing the anxiety levels and various personal opinions and practices regarding the pandemic was sent to the PKU patients managed at our clinic, who were 12 years of age or older. Ninety-eight patients responded to the questionnaire. Median age of the participants was 19 years.

Results. Most patients were compliant with the hygiene and social distancing recommendations regarding the spread of COVID-19. Of the patients, 61.2% felt more anxious since the pandemic. The most common concern was the possibility of not being able to obtain special nutritional products (58.2%). Anxiety level was significantly higher in females.

Conclusions. These data suggest that food security is an important issue of concern in PKU patients. In line with the changing world after the pandemic, different strategies should be considered in the management of patients with inborn errors of metabolism, including PKU.

Key words: COVID-19, phenylketonuria, anxiety.

Phenylketonuria (PKU) is an inherited disorder of the breakdown pathyway of the amino acid phenylalanine.[1] The resulting accumulation of phenylalanine causes intellectual disability and many other neuropsychiatric symptoms.[2] Treatment must be initiated soon after birth and maintained lifelong, usually utilizing a phenylalanine-restricted diet to keep the blood phenylalanine level within a target range.[3] Turkey has the highest incidence of PKU, at least partly due to the high rate of consanguinity.[4] The newborn PKU screening program in Turkey, initiated by our department as a pilot study in 1986, became a national screening program in 2006.[5-7]

It is widely observed that adherence to dietary treatment is very good in childhood, but decreases thereafter, especially after adolescence, with phenylalanine levels exceeding the target levels. In fact, 31.1% of the PKU patients in our clinic are poorly compliant to their dietary treatment.[7-9] The diet is extremely challenging for the patients and their families, and often creates significant psychosocial and financial problems.[10-13] Patients have difficulties in maintaining their diet at school and work, and experience anxiety and low self-esteem.[14,15] Patients with PKU have a higher risk of psychiatric illness and cognitive impairment, even if they are treated early and

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Received 8th March 2021, revised 31st March 2021, accepted 2nd April 2021.

effectively.[16] Prevalence of neuropsychiatric symptoms such as carelessness, hyperactivity, depression and anxiety in PKU are above the general population estimates. Neuropsychiatric symptoms and executive dysfunction have been demonstrated to correlate with phenylalanine levels.[17]

COVID-19, the disease caused by SARS-CoV-2 was declared a pandemic by the World Health Organization on March 11, 2020. As of March 30, 2021, 3,277,880 confirmed cases and 31,385 deaths have been reported in our country. The elderly seem to develop more serious diseases and hypertension, cardiopulmonary diseases, cancer and diabetes are additional risk factors.[18-20] In order to prevent the spread, staying at home and social isolation is encouraged, social activities have been canceled or postponed, and commercial activities were temporarily suspended or restricted in many countries.[21] It is not surprising that such devastating alterations to social and economic life have had significant psychological impact on people all over the world. For example, in a general population study on the COVID-19 pandemic in India, the prevalence of anxiety and depression has been shown to increase.[22] In the United Kingdom, pandemic-related anxiety, depression and trauma were shown to be associated with an underlying disease.[22] There are not many studies on how patients with rare diseases are affected by this pandemic. However, in a study conducted in Italy in April 2020, 49% of patients receiving enzyme replacement therapy were reported to have pandemic-related disruptions in their treatment.[23] National initiatives such as the French Rare Diseases Health Care Network for Neuromuscular Diseaeses (FILNEMUS) have sought to draw a path for how to track and manage patients with rare diseases.[24] Similarly, patients with PKU may be affected by humanitarian, social and economic fluctuations due to their special needs. From this point of view, one may wonder how patients with PKU, a rare disease that may predispose them to neuropsychiatric findings such as anxiety, are coping with this pandemic. Therefore, we aimed to evaluate how they were affected by the COVID-19 pandemic, and assess their anxiety levels.

Material and Methods

This cross-sectional, observational study was carried out at the Pediatric Metabolism Unit of Hacettepe University İhsan Doğramacı Children's Hospital, which is one of the largest metabolic centers in the region, and follows patients from all around Turkey, predominantly from Central Anatolia. Classical PKU patients 12 years of age and older who were actively followed in our clinic (came to at least one routine outpatient follow-up visit within the past year) were included in the study. In order to adhere to the social distancing efforts, patients in our center were contacted via telephone or social media, and questionnaire forms were delivered via Google Forms to the eligible patients followed at our center, and data was collected from the forms filled and submitted back by the patients anonymously. Written informed consent was obtained from the patients before participating in the online study.

As there were no validated self-report anxiety scales developed in relation to the COVID-19 pandemic, we sought to adapt a validated tool to the task at hand in order to formulate a questionnaire. The commonly used Beck Anxiety Scale consists of 21 questions and is fit for face-to-face application.[25] Since face-to-face interviews were not applicable in the pandemic conditions, the scale needed to be condensed and simplified, so that it could be well understodd by an average older PKU patient with short attention span and possibly mildly impaired executive functions. The questionnaire was developed by physicians specialisng in metabolic disorders and clinical psychologists with years of experience with PKU patients. In summary, the questionnaire included structured questions adapted from Beck Anxiety Scale, encompassing demographic data, medical information, and self-reported

anxiety, using short text answers, multiple choice and open-ended questions. Except for questions that inquired about demographic data, all questions were explicitly worded to inquire thoughts, feelings and practices in the last 15 days. The online questionnaire was sent out on 31 March 2020, and data collection was terminated on 1 June 2020.

The data obtained in the study were evaluated with SPSS (Statistical Package for the Social Sciences) version 21. Descriptive statistics, categorical variables were shown with numbers and percentages, and numerical variables with mean, standard deviation, median, range and interquartile range (IQR). Kolmogorov-Smirnov Test was used to assess normality of distributions. Mann Whitney U and Kruskal Wallis tests were used in comparing two and more independent groups, respectively. Chi-square and Fisher exact tests were used in the analysis of categorical variables. Spearman correlation test was used in the correlation analysis. Instances where the type-1 error level is below 5% ($p < 0.05$) were considered statistically significant. Hacettepe University Ethics Board for Non-interventional Clinical Studies approved the study (Approval Date: 31 March 2020 Issue: 2020/07-20).

Results

The questionnaire forms were sent out to 347 patients, 98 of whom (28.2% of all eligible patients) participated in the study by returning the filled out forms. The demographic information of the patients is summarized in Table I. Of the patients, 50% (n = 49) were female. The median age of the participants was 19 years (range:12-51 years). A median of four people resided in the household (IQR=2). Fifteen patients had comorbidities (three had hypothyroidism, and one each had anxiety disorder, osteoporosis, heart failure, ulcerative colitis, hereditary fructose intolerance, epilepsy, attention deficit and hyperactivity disorder). Of the patients 86.6% were being treated with phenylalanine restricted diet. All 41 patients

Table I. Clinical and demographic data of the study group (N=98).

	n	%
Gender		
Male	49	50
Female	49	50
Civil status		
Lives with spouse/partner	21	21.4
Single	74	75.4
Divorced	3	3.1
Working status of patients		
Working constantly	28	28.6
Not working	70	70.4
Modality of treatment		
Phenylalanine restricted diet	84	86.6
Other	8	8.2
Does not comply with diet / treatment	5	5.2
Presence of additional chronic disease	15	15.3
Working status of mother		
Working constantly	15	15.3
Not working	82	83.7
Not specified	1	1
Working status of father		
Working constantly	71	72.4
Not working	25	25.5
Not specified	2	2
Living with an individual over the age of 65	11	11.2
Living with another patient with phenylketonuria	13	13.3
Media for social contact with acquaintances during pandemic		
Face to face contact	16	16.10
By phone	52	53.10
By video call	33	33.7
Internet based systems	38	38.8
Via social media	33	33.7
Distribution of the sources from which patients received information during the COVID-19 pandemic		
Television broadcasts	80	81.6
Physician's opinion	17	17.3
Internet broadcasts	51	52
Family members	47	48
Friends	12	12.2
Other	3	3.10

under the age of 18 attended school. Among the remaining 57 patients older than 18 years, 25 (43.8%) had a steady job.

Of the patients 76.5% (n = 75) stated that they had social contact with friends during the pandemic. Most of the patients (53.1%) contacted their friends over the phone.

Patients were asked if their knowledge level about the COVID-19 pandemic was sufficient. Of the patients 67.3% (n = 66) stated that they had sufficient information about the pandemic. The patients were also asked what their sources of information were. The majority of patients (81.6%) stated that they learned about the pandemic via television, followed by internet broadcasts (52%).

The self-reported anxiety levels of the patients are given in Table II. Of the participants , 61.2% reported that they felt more anxious since the pandemic. The biggest concern of the patients was the possibility of not being able to obtain special nutrition products (58.2%). Of the patients 79.6% (n=78) described at least one sign of anxiety. Of the participants , 21.4% stated that they had difficulty in dealing with anxiety. Female participants significantly more commonly reported that they had difficulty coping with anxiety since the onset of the pandemic (37.2% vs. 10.4%, p=0.010), felt sad or unhappy (59.6% vs. 36.2%, p=0.023), worthless (19.1% vs. 4.3%, p=0.025), scared without reason (75.6% vs. 46.9%, p=0.005), and had palpitations unrelated to physical activity (21.7% vs. 6.1%, p=0.027).

The precautionary measures taken by patients against the COVID-19 pandemic were also inquired. The patients' responses are summarized in Table II. Patients mostly paid attention to hygiene recommendations (66.3%). Of the participants 55.1% fully complied with the rule of staying at home.

The patients were asked to give their anxiety levels a score from 1 to 5. Self-reported anxiety levels and age, gender, source of information, level of knowledge, and treatment modality were compared (Table III). No statistically significant results were obtained, except for gender. Anxiety level was higher in females than in males. Age was not significantly correlated with anxiety levels (Spearman's correlation coefficient ϱ=0.085, p=0.413). No statistically significant relationship was found between the source of the information about pandemic and the level of anxiety.

Before the participants participated in the survey, their consent was obtained online.

Discussion

The COVID-19 pandemic affected the world as well as our country, and our patients. We wanted to investigate the concerns of a vulnerable and rare patient population in this difficult process and the factors that may influence this anxiety, using a web-based study, befitting the new norms of communication during this unprecedented pandemic.

The time frame of this study coincides with the initial stages of the pandemic response in Turkey. On 11 March 2020, the first cases of SARS-CoV-2 detected in Turkey was announced by the Ministry of Health. The first COVID-19-related death occurred on March 15, 2020. The Ministry of Health announced on April 1, 2020 that coronavirus cases were seen in all regions of the country. As of March 13, 2020, restrictions were gradually imposed on foreign entries and exits. As of March 16, 2020, restrictions have been placed on social-cultural-religious meetings within the country. On April 3, 2020, a curfew was imposed across the country for those born later than December 31, 1999, masks were imposed in public areas such as markets, and entrances and exits to 30 metropolitan cities were halted for 15 days. Curfews of different days and lengths were declared as of April 10, 2020. The easing of the initial restrictions did not ocur until June 1, 2020, which coincides with the end of data collection for this study. In other words, the data was collected at a time when the scientific information was premature,

Table II. Anxiety level assesments of patients and evaluation of the measures taken by patients during COVID-19 pandemic.

	n	%
How did your anxiety change during the pandemic?		
Decreased	3	3.1
Did not change	34	34.7
Increased	60	61.2
What are your concerns about the pandemic?		
I feel more at risk than the general population	55	56.1
I think I am at risk of having problems accessing healthcare services	41	41.8
I think I may have difficulties in accessing special nutrition products	57	58.2
I think I may have difficulty in accessing medicinal products	41	41.8
I think I'm more likely to get infected	53	54.1
I think that if I get infected, I will be seriously ill	49	50
I think one of my family members will get sick	28	28.6
Other	14	14.3
How was your last 15 days since the pandemic started?		
Partially coped	27	27.6
Neutral	43	43.9
Difficult to deal with	21	21.4
Not specified	7	7.1
I felt unhappy and sad		
Yes	45	45.9
No	49	50
Not specified	4	4.1
I felt worthless		
Yes	11	11.2
No	83	84.7
Not specified	4	4.1
I had a hard time taking the first step to do a job		
Yes	27	27.6
No	64	65.3
Not specified	7	7.1
Sometimes I feel scared even though it doesn't have a logical explanation		
Yes	57	58.2
No	37	37.8
Not specified	4	4.1
I had difficulty breathing even though I did not do a physical activity		
Yes	9	9.2
No	85	86.7
Not specified	4	4.1
I felt my heart beating fast even though I was not doing any physical activity		
Yes	13	13.3
No	82	83.7
Not specified	3	3.1

Table II. Continued.

	n	%
I feel that I am more sensitive		
Yes	13	13.3
No	82	83.7
Not specified	3	3.1
I tend to overreact to events		
Yes	35	35.7
No	59	60.2
Not specified	4	4.1
What would your score be if you scored 1 to 5 on the level of anxiety the pandemic created in you?		
1-I'm not worried at all	9	9.2
2- I'm less concerned	21	21.4
3-I'm concerned	41	41.8
4-I'm very worried	22	22.4
5-I can't deal with my anxiety	3	3.1
Have you experienced an event or events today that caused your anxiety to increase?		
Yes	33	33.7
No	31	31.6
Not specified	34	34.7
What COVID-19 precaution measures are you taking?		
I pay attention to hygiene.	65	66.3
I try to follow social isolation rules.	59	60.2
I am trying to strengthen my immune system.	9	9.2
Do you follow the rule of staying at home?		
I comply fully	54	55.1
I rarely go out (eg only for the market)	41	41.8
I don't follow the rule of staying at home	2	2
Not specified	1	1

daily news were concerned primarily with the pandemic and even the short-term future was full of uncertainties. The stressful time in which the study was conducted might have contributed to the high anxiety levels reported in the study questionnaire.

The majority of the participants reported at least some adherence to their diet, and many of them managed to maintain social contact with peers, mostly over the phone. Of participants 81.6% received information about the pandemic via television and 52% via the internet. Although new media platforms come to the fore, it is worthy to note that, at least in this patient population, television broadcasting still has a very important effect. Only 17.3% of the patients received information from a physician. This low rate may have resulted from the decrease in routine physician or hospital visits during the pandemic. It may be difficult to achieve the classical patient-physician relationship in the pandemic, when face-to-face interactions are avoided unless absolutely necessary. Telemedicine practices in many different disciplines were strongly discussed in the pandemic process.[26-29] It is necessary to mention the critical role of social media and mass media in the acquisition of information in this process. However, this has some drawbacks. In a study

Table III. Comparison of pandemic-related anxiety levels of patients in terms of gender, knowledge level, measures taken and treatment modalities.

	COVID-19 self-reported anxiety state					p
	1+	2+	3+	4+	5+	
Gender						0.002*
Male	6(12.5%)	15(31.3%)	20(41.7%)	7(14.6%)	0(0%)	
Female	3(6.3%)	6 (12.5%)	21(43.8%)	15(31.3%)	3(6.3%)	
Age						0.602
< 18 years	4(10%)	8(20%)	20(50%)	8(20%)	0(0%)	
≥ 18 years	5(9.1%)	13(23.6%)	21(38.2%)	13(23.6%)	3(5.5%)	
Pandemic subjective knowledge level						0.0990
Enough	6(9.1%)	11(16.7%)	35(53%)	13(19.7%)	1(1.5%)	
Not enough	3(10%)	10(33.3%)	6(20%)	9(30%)	2(6.7%)	
Compliance with lockdown						0.487
Fully compliant	8(14.8%)	11(20.4%)	21(38.9%)	12(22.2%)	2(3.7%)	
Rarely goes out	1(2.5%)	9(22.5%)	19(47.5%)	10(25%)	1(2.5%)	
Non-compliant	0(0%)	1(50%)	1(50%)	0(0%)	0(0%)	
Measure taken						0.616
Paying attention to hygiene	7(10.9%)	16(25%)	24(37.5%)	14(21.9%)	3(4.7%)	
Following social isolation	4(6.9%)	14(24.1%)	27(46.6%)	13(22.4)	0(0%)	
Trying to strengthen immune system	1(11.1%)	2(22.2%)	2(22.2%)	4(44.4%)	0(0%)	
Treatment modality						0.769
Phenylalanine restricted diet	8(9.5%)	21(25%)	34(40.5%)	18(21.4%)	3(3.6%)	
Other	0(0%)	0(0%)	6(75%)	2(25%)	0(0%)	
Does not comply with diet / treatment	1(25%)	0(0%)	1(25%)	2(50%)	0	
Source of information about COVID-19 pandemic						
Television broadcasts	6(7.6%)	16(20.3%)	34(43.0%)	20(25.3%)	3(3.8%)	0.425
Physician's opinion	1(5.9%)	5(29.4%)	9(52.9%)	2(11.8%)	0(0%)	0.651
Internet broadcasts	2(4%)	11(22%)	21(42%)	15(30%)	1(%2)	0.198
Family members	3(6.5%)	11(23.9%)	17(37%)	14(30.4%)	1(2.2%)	0.406
Friends	0(0%)	5(41.7%)	4(33.3%)	3(25%)	0(0%)	0.425

* $p<0.05$

+ 1-I'm not worried at all
2- I'm less concerned
3-I'm concerned
4-I'm very worried
5-I can't deal with my anxiety

conducted in Turkey, Youtube videos related to the COVID-19 pandemic were examined. Video contents were audited and only 37.5% were found useful. Of those evaluated 15.8% of Turkish and 10.4% of English videos were found to have false/misleading information.[30] It may be possible to use social and new media tools to our advantage to alleviate anxiety during an epidemic. It is important to use and produce accurate, reliable and reputable sources of information.[31,32]

Of the patients in the study group 61.2% stated that their anxiety increased during the pandemic, 45.9% were unhappy and upset, 11.2% felt unworthy and 35.7% stated that they

overreacted to events. It is noteworthy that these and similar symptoms of depression are present in the study group. In the COVID-19 pandemic, many health-care workers showed signs of anxiety and depression.[33] Similarly, anxiety levels in the general population have also increased.[15,22,34,35] However, such studies addressing patients with rare diseases have been lacking, which has motivated us to perform this study.

The most common concern of the patients (58.2%) was the possibility of not being able to obtain special nutrition products. It is known that many people around the world stock food with the concern that they may not be able to find basic food items.[36,37] It is not surprising that PKU patients experience a higher anxiety regarding access to food because they acquire their medical foods from pharmacies, or they already have financial or logistic difficulties in obtaining their special low-protein food products.[38,39] This additional burden is unique to patients with PKU and with other rare inborn errors of metabolism requiring special diets. It is important to advocate for policies that ensure food and medicinal product security in this vulnerable patient population suffering from rare, orphan diseases. It is also concerning that Turkey is dependent on import of medical foods and drugs, especially in the rare diseases group. In particular, the possibility that the closure of the borders would disrupt the global logistics chain and/or cause a decrease in production capacities probably contributed to the anxiety of the participants.

In our study, pandemic-related anxiety levels were more common in females. This may be significant in terms of gender preference of anxiety symptoms in the general population.[40] In the literature, it has been shown that clinical findings of anxiety appear during adolescence and early adulthood.[41] However, when the distribution of anxiety levels in terms of age was examined in our study, no statistical difference was found. This may be related to the fact that the participants were all older than 12 years.

Our study has its limitations. Since the questionnaires were not completed via a face-to-face interview and the patients are asked to complete the questionnaire themselves, it is not known whether the patients understood the questions completely. In addition, the patients self-expressed their anxiety levels and knowledge levels. Performing face-to-face mental state examinations to assess anxiety more objectively was not feasible. As the filled questionnaires were returned anonymously, researchers were blinded to the identities of the participants, making it impossible to correlate the answers with clinical data.

Since the COVID-19 pandemic is a process full of unknowns, and was especially so in the initial stages, it cannot be denied that there were many questions raised in the inborn errors of metabolism patient community. We had the opportunity to observe this both during the study and while providing patient service. In the beginning, the questions mainly concerned whether they would be sick more easily than the society and what their prognosis would be if they were sick. So far, there has been no indication that people with PKU may be under higher risk of infection, or of more severe disease. The results of this study show that the level of COVID-19 pandemic-related anxiety was high in patients with PKU, and significantly higher in females. Food insecurity regarding medical and low-protein foods was a major concern, which was not an issue previously addressed in the literature. Our study suggests that different support strategies should be brought into the spotlight by taking into consideration the changing world and medical practices in the post-COVID-19 era. Especially, in new communication channels such as social media and the internet, it may be useful to open areas where health care providers can provide patients with reliable information, and share their concerns and problems. In addition, guaranteeing the supply chain of food and medicinal products in cooperation with the local authorities may reduce the anxiety levels.

This may also applicable to other rare metabolic disorders requiring special diets. In this respect, monitoring of inborn errors of metabolism patients with telehealth applications should be discussed in the community. At this point, the contribution of patients, families and non-governmental organizations cannot be overemphasized.

Acknowledgment

We would like to thank our patients, their families, patient and family associations. Their support has always been with us.

Ethical approval

Hacettepe University Ethics Board for Non-interventional Clinical Studies approved the study (Approval Date: 31 March 2020 Issue: 2020 / 07-20).

Author contribution

The authors confirm contribution to the paper as follows: study conception and design: HTA, YK, AD, AT, TC SS; data collection: HTA, KÇ, ABK, İE; data analysis and interpretation: HTA, YK, YY, SS; drafting of manuscript: HTA, YK, YY; critical review of manuscript: YY, AD, AT, TC, SS. All authors approve and take responsibility for the final version of the manuscript.

Source of funding

The study did not received funding.

Conflict of interest

The authors declare no conflict of interest.

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