Unmet Needs of Children with Inherited Metabolic Disorders in the COVID-19 Pandemic

Ezgi Özalp Akın, Fatma Tuba Eminoğlu, Neslihan Doğulu, Merve Koç Yekeduz, Ummuhan Öncül, Funda Akpınar, Gamze Hayran

What is already known on this topic?
- The unmet needs of children with rare inherited metabolic disorders (RIMDs) pose serious consequences.
- The coronavirus disease 2019 (COVID-19) pandemic negatively influenced the needs of children with RIMDs.
- Unmet needs of children with RIMDs in low- and middle-income countries during the COVID-19 pandemic based on a framework have not been studied.

What this study adds on this topic?
- All children with RIMDs had at least 1 unmet need from Turkey.
- The most prioritized needs were in health care, whereas the most common were in special services and rehabilitation.
- The needs of children with RIMDs from low- and middle-income countries should be addressed in this and possible future crises.

ABSTRACT

Objective: Crucial information is lacking on unmet needs of children with rare inherited metabolic disorders during the coronavirus disease 2019 pandemic from low- and middle-income countries. We aimed to identify the unmet needs of children with rare inherited metabolic disorders from Turkey.

Materials and Methods: In a cross-sectional observational design, all children with rare inherited metabolic disorders aged 0–18 years followed at Ankara University School of Medicine Department of Pediatrics Pediatric Metabolism Division were recruited and interviewed via phone calls. The Expanded Guide for Monitoring Child Development enabled assessment of unmet needs and environmental context during coronavirus disease 2019 pandemic. Step-wise logistic regression analysis was used to determine independent factors associated with unmet needs.

Results: The sample comprised 229 children (54.1% boys) with rare inherited metabolic disorders (36.7% diet-dependent disorders). Most common diagnoses were amino acid metabolism disorders (40.2%). Of all, 29.3% of the mothers reported depression, 25.3% loss of job of family members during the pandemic. All children had unmet needs: at least 73.0% in health care, 96.8% in education, 78.3% in special services/rehabilitation. Having significant developmental delay and/or disability (odds ratio = 2.31, 95% CI: 1.14-4.67) emerged as the only independent factor associated with unmet needs in health care.

Conclusion: Children with rare inherited metabolic disorders and their families in Turkey experience unmet needs in many domains during coronavirus disease 2019 pandemic. Urgent action is needed to address the unmet needs of children with rare inherited metabolic disorders, especially those who have significant developmental delays and/or disabilities for this pandemic and possible future crises.

Keywords: Metabolism inborn errors, disability, health services needs and demand, unmet needs, child, COVID-19

INTRODUCTION

Rare inherited metabolic disorders (RIMDs) are a group of disorders for which the incidence of each disorder is rare but the cumulative incidence is estimated to be 1 per 800–2500 live births with a higher incidence in countries with a high rate of consanguinity between parents. It is well known that the children with RIMDs have specific needs such as close follow-up, ongoing health management, education, intervention, and rehabilitation services. “Unmet needs” is a construct used to capture the degree to which needed services are not received and a critical indicator of problems of access to health care and other services. The unmet needs of children with RIMDs pose serious consequences. Children with RIMDs from both

Cite this article as: Özalp Akın E, Tuba Eminoğlu F, Doğulu N, et al. Unmet needs of children with inherited metabolic disorders in the COVID-19 pandemic. Turk Arch Pediatr. 2022;57(3):335-341.
high-income and low- and middle-income countries (LMICs) had unmet needs before the pandemic. Studies in the past years from mostly high-income countries have shown that the coronavirus disease 2019 (COVID-19) pandemic has negatively influenced the needs of both adults and children with a variety of rare diseases like immune deficiencies, genetic disorders. Information is urgently needed specifically on the unmet needs of children with RIMDs during the COVID-19 pandemic, particularly in LMICs where the majority of such children reside.

Knowing the unmet needs of children with RIMDs is crucial to plan actions in this pandemic and other crisis in the future. Failure to obtain timely treatment may predispose metabolic decompensations, affect developmental functioning, and even cause lifelong disability and death. Multicenter studies including children with RIMDs during the COVID-19 pandemic have found that children and their families experienced difficulties in accessing health care, medications, and timely treatment, however, have not examined all needs of these children like education, rehabilitation, and special services using the holistic framework proposed by the United Nations Convention on the Rights of the Child, stating that every child needs to live, survive, develop to optimal potential, and have education.

Turkey is a middle-income country that has a relatively high rate of RIMDs due to the high rate (24%) of consanguinity between parents. In the Turkish health care system, all children have health insurance to access health care, and children with documented RIMDs are eligible for government-subsidized disability services.

We aimed to determine the unmet needs of children with RIMDs during the COVID-19 pandemic to examine which needs are priority and to examine associated child-, family-, and environment-related factors using a comprehensive framework.

**MATERIALS AND METHODS**

**Study Design and Participants**

In Turkey, the first COVID-19 case was reported on March 11, and first death was recorded on March 17, 2020. The first lockdown period was established between March 17 and July 1, 2020, to minimize the transmission and mortality. In this lockdown period, all international travels were shut down, domestic travels were limited, and most public places and businesses were closed. Nonurgent outpatient clinic services were suspended, and schools, special education, and rehabilitation centers were also suddenly closed. During this period, daily number of deaths due to COVID-19 have changed between 30 and 127. At the end of the lockdown period, 204 610 COVID-19 cases and 5206 deaths were reported according to the reports of Turkish Ministry of Health.

This cross-sectional, observational study was conducted by Ankara University Department of Pediatrics, Pediatric Metabolism Division and Developmental Pediatrics Division which are located in a large tertiary hospital in the capital of Turkey and collaborate closely to provide a holistic biopsychosocial approach to and services and advocacy for children with RIMDs and their families. All children aged 0–18 years who had been followed at Ankara University School of Medicine Department of Pediatrics, Pediatric Metabolism Division with the diagnoses of RIMDs between July 1, 2012, and March 1, 2020, were recruited.

**Procedures**

We assessed the unmet needs of children with RIMDs using a telephone interview that was conducted between September 15 and October 15, 2020. Five clinicians from the study center called on the telephone, and children were included if their parents provided informed consent to participate in the study. Over the telephone, the clinicians conducted a semi-structured interview lasting approximately 30 minutes regarding their difficulties and needs specifically in the lockdown period between March 17 and July 1, 2020. Up to 4 phone calls were placed to reach the family and if the mother did not respond to any of these calls, the case was categorized as “non-respondent.” During the phone call interview, questions of the Expanded Guide for Monitoring Child Development (Expanded GMCD) were read to the mother and the answers were recorded in audio by the researchers. Information related to the health conditions of the child such as the diagnoses, medications, specific diet requirements, and presence of disabilities including intellectual disability, motor disability, speech and language disorder, autism spectrum disorder, and significant developmental delays were determined from the medical records.

The study was approved by the Ethics Committee of the Ankara University (Decision number: 18-483-20, October 09, 2020).

**Measures**

We used the Expanded GMCD during the telephone interview, which is a written questionnaire based on the World Health Organization International Classification of Functioning, Disability and Health and Nurturing Care frameworks and provides information on health conditions, developmental functioning, activities and participation, as well as the environmental factors including needs and unmet needs. This tool was developed particularly for children with special health care needs, and the questions are well known to be understood and answered by caregivers with low education levels. Furthermore, in a larger study of children with special needs, there was evidence that the Expanded GMCD questions were accepted and answered by the parents of children with RIMDs.

The “COVID-19-specific unmet needs” were defined as needs that were met before the pandemic and were not met during the COVID-19 pandemic. For the purposes of this study, the “Service needs” and “Environmental factors” sections of the Expanded GMCD were modified to include issues related specifically to the COVID-19 pandemic and children with RIMDs. Pandemic-related questions were asked to the families specifically for the lockdown period. The questions probing unmet needs in health care services were modified in relation to children with RIMDs and included access to health care, support for specific dietary needs, medicine and/or enzyme prescriptions all of which were government subsidized and provided before the pandemic. Family- and environment-related factors were examined by adding pandemic-related questions to the “Environmental factors” section of the Expanded GMCD. These included changes of primary caregivers, feelings of increased fatigue in caregivers, loss of job, decrease in monthly income,
COVID-19 infection, and COVID-19-related death in the family. These factors were asked as structured questions and coded as “present” or “absent.” Of the unmet needs identified, we asked the respondent which of the following were priority unmet needs during the pandemic: health care, education, special services, rehabilitation, disability monetary benefits, or other needs they mentioned.

**Data Analyses**
Descriptive statistics were given in frequencies for categorical data, as means and standard deviations for normal continuous distributions, and as medians and interquartile ranges (IQRs) otherwise. The Shapiro–Wilk test was used to check whether there was a normal distribution of the numerical variables. Based on bioecological theory, we hypothesized that the priority unmet needs of the child would be associated with child-, family-, and environment-related factors. The child-related categorical variables examined were sex, age, diet-dependent metabolic disorder, having a significant developmental delay, and/or disability. Family- and environment-related categorical variables included living in a nuclear family, residing outside the capital city (Ankara), the mother reporting depression during pandemic, income level, loss of job in the household family members during the pandemic, decrease in monthly household income during the pandemic, change in primary caregiver during the pandemic, maternal and paternal education, and COVID-19 infection in the family members. Using chi-square test, we examined whether the categorical variables listed above were associated with unmet needs in health care services. Next, multivariable logistic regression analysis was applied via entering the variables with P values <.20 in the bivariate analysis into a model to determine independent factors associated with the dependent variable (presence of unmet needs in health care services). Odds ratios (ORs) and 95% CIs were computed. For statistical significance, 95% CIs were used. Statistical analyses were conducted using the Statistical Package for Social Sciences, version 20.0 software (SPSS Inc.; Chicago,IL, USA).

**RESULTS**
A total of 290 patients with RIMDs were eligible for this study. Of these, 48 did not respond to the phone calls, 9 had died since their last follow-up, and 4 did not provide consent for the study. The remaining 229 (79.0%) children comprised the study sample. Most children (80.3%) had disabilities and/or significant developmental delays in at least 1 domain of development. The sociodemographic characteristics of the children are shown in Table 1. The median age was 5.3 (IQR: 2.8–8.3) years, and most were boys (54.1%). The most common disorders were amino acid metabolism disorders followed by mitochondrial, lysosomal and peroxisomal, organic academia, and carbohydrate metabolism disorders. Eighty-four (36.7%) children required lifelong specific diet for maintenance treatment. Parental consanguinity was present in 141 (61.6%) children. Most mothers were homemakers (87.3%). Most household incomes were less than minimal wage, 8 (3.5%) had no household income, and 25 (10.9%) families did not want to share their household income. Twenty-nine mothers (12.7%) were working on a job. Approximately half (55%) of the families were residing in Ankara and the rest were from 42 different cities of Turkey.

**Coronavirus Disease 2019 Pandemic-Related Environmental Factors**
The COVID-19 pandemic-related factors affecting the child and family are summarized in Table 2. Almost all mothers (98.7%) and fathers (84.5%) were at home with their children during the COVID-19 pandemic lockdown period. Coronavirus disease 2019 infection occurred in 43 child’s families and 1 child lost his grandfather. None of the children were infected with COVID-19.

**Services Received Before the Pandemic and Unmet Needs During the Pandemic**
Services received before the pandemic and the unmet needs that arose during the pandemic are summarized in Table 3. Before the pandemic, all children were accessing health care as needed, most (77.7%) were receiving their prescriptions regularly, and 73.7% had obtained a special needs report which made them eligible for special services. Educational services before the pandemic were accessible for the majority (91.7%) of school-aged (7-18 years) children: 73.8% of the 84 children in the school age group had been included in mainstream education, 17.9% had been receiving special school education, and 8.3% been receiving no education. Of the 97 children in the preschool age range (24–72 months), 28.8% had been receiving preschool education. All of the children had at least 1 unmet need in one of the service domains. When mothers were asked to prioritize unmet needs, most (54.1%) prioritized unmet health care needs. Education, special services/rehabilitation, and financial needs were prioritized by 24.9%, 9.6%, and 8.3%, respectively. Additionally, 3.1% of the mothers prioritized social needs of their child like meeting friends. A total of 167 (73.0%) of children had unmet needs in health care services. Of the children requiring specific medicine prescription, 63.5% could not receive. Of these, 10 of 19 children (52.6%) with lysosomal storage diseases could not receive their enzyme replacement treatment timely. Of 84 children requiring support for their specific diet, 60.7% did not receive these subsidies. Most of the children who had received education services before the pandemic had unmet needs in the mainstream education (96.8%), special school (93.3%) and preschool education (92.3%) services during the pandemic. Some private centers continued educational/rehabilitation services through video phone calls or zoom sessions. As a result, 7 (29.1%) children received distant speech and language therapy, 5 (6.0%) special education, and 8 (13.6%) physiotherapy. Thirty-nine families (17.3%) reported that their children received distant home-based early intervention provided by Developmental Pediatrics Division by telehealth during the study period. None of the 7 children who had received vision, hearing, and ergo-therapy interventions before pandemic was able to receive these services from a distance.

All 170 families that were receiving disability benefits including monetary support from the government and various discounts due to their child’s special needs prior to the pandemic said that this support had continued. Ninety-six (41.9%) families stated that they needed additional financial support: 33 (34.4%)
of these families stated that they lacked sufficient food and clothing for the child. Of 31 children who received diaper subsidization before the pandemics, most (58%) could not receive this need during the pandemic.

The associations of child-, family-, and environment-related factors with having unmet health care needs are given in Table 4. In the logistic regression model, having a significant developmental delay and/or disability (OR = 2.31, 95% CI: 1.14–4.67, P = .020) emerged as the only independent factor associated with unmet needs in health care needs.

DISCUSSION

This study provided information on the unmet needs of children with RIMDs during COVID-19 pandemic in a middle-income country, Turkey. In this referred sample of children with various inherited metabolic disorders from all regions of the country, all children had at least 1 unmet need in the service domains examined. The unmet need prioritized by the families during the pandemic was health care, whereas the most common unmet needs were special services and rehabilitation. These findings have important implications for clinicians and policymakers in addressing the needs of this vulnerable population during the pandemic and beyond.

A recent thematic study has reported the impact of the pandemic on RIMDs from 10 countries in Asia Pacific region. In this study, the most important difficulty encountered by patient organizations was access to medical care parallel to our result and 58% of children with RIMDs had problems in access to medications. A study by the European Reference Networks for Hereditary Metabolic Diseases (MetabERN) has included survey data of 39 patient organizations from 18 European countries. Approximately half of the patient organizations reported changes in health care services; 33% reported that treatments for the rare diseases were discontinued and that 25% of the children had problems in accessing their medications. Both regional studies reported that most children on a restrictive diet had difficulties in regulating their diets. As outpatient appointments were postponed, regular blood samples needed for monitoring could not be obtained to regulate diets. A study from Ireland showed that 53% of the scheduled appointments were cancelled. The reported unmet health care service needs are lower in these studies than the 73% we have found in our study. Another study from Turkey reported on 75 patients with lysosomal storage disorders and reported similar missed enzyme treatment rates (46.6%) to our study (52.6%) during the pandemic. It should be noted that even before the pandemic children with lysosomal storage disorders from a similar tertiary care center, Turkey had high levels of missed enzyme treatments (63.0%). It seems that missed enzyme treatments may be explained by socioeconomic and health system difficulties regarding children with complex health care needs rather than only pandemic-related difficulties for Turkey. Missed enzyme replacement treatments were reported higher than MetabERN study (42%), as in Turkey home treatment was not possible before the pandemics and children had to attend hospital for such treatment. It appears that the sudden onset of the COVID-19 pandemic affected both high-income and LMICs in providing health care services to children with RIMDs during the early months of the pandemic.

were already receiving financial support from the government and stated that this was not enough for their child’s needs, 63 (65.6%) had not been found to be disadvantaged enough for government-paid financial support before the pandemic. One

| Table 1. Sociodemographic Characteristics and Diagnoses (N = 229) |
|---------------------------------------------------------------|
| **Characteristics of children**                                |
| Boys              | 124 | 54.1 |
| Girls             | 105 | 45.9 |
| **Age (years)**    |     |      |
| 0–3               | 82  | 35.9 |
| 4–6               | 63  | 27.5 |
| 7–12              | 69  | 30.1 |
| 13–18             | 15  | 6.5  |
| **Diagnoses**     |     |      |
| Aminoacid metabolism disorder      | 92  | 40.2 |
| Mitochondrial disorder             | 30  | 13.1 |
| Lysosomal and peroxisomal disorder | 29  | 12.7 |
| Organic acidemias                | 22  | 9.6  |
| Carbohydrate metabolism disorder  | 17  | 7.4  |
| Neurometabolic disease            | 4   | 1.7  |
| Congenital glycosylation disorder | 4   | 1.7  |
| Fatty acid oxidation disorder     | 3   | 1.3  |
| Urea cycle defect                | 2   | 0.9  |
| Other                          | 26  | 11.4 |
| Children with a disability and/or significant developmental delay | 184 | 80.3 |

| Table 2. COVID-19-Related Environmental Factors |
|------------------------------------------------|
| **Family- and environment-related factors**    |
| Decrease in monthly household income           | 100 | 43.7 |
| Mother reporting increased fatigue             | 100 | 43.7 |
| Mother reporting depression                    | 67  | 29.3 |
| Loss of job of family members                  | 58  | 25.3 |
| COVID-19 infection in family                   | 43  | 18.8 |
| Change in primary caregiver                    | 28  | 12.2 |
| Father reporting depression                    | 24  | 10.5 |
| COVID-19, coronavirus disease 2019.            |     |      |
Reports from many countries from Europe, Asia, Africa, South, and North America imply that some countries rapidly implemented telemedicine and home care services to overcome this issue.\textsuperscript{15,24-26} For example, in Italy, after a telehealth visit, nurses visited patients at their homes to draw blood samples if needed.\textsuperscript{25} Although, the study by Zubarioglu et al\textsuperscript{27} from Turkey has shown that telemedicine can be used effectively for follow-up and management of children with rare metabolic disorders, more than 1 year after the pandemic, the telemedicine system has not been incorporated into the health care system in Turkey. Similar to a report from another individual center in Turkey,\textsuperscript{28} we reached out to the patients through our own efforts. As reflected in our high unmet needs results, we were unable to counter the effects of the deficiencies in the health system.

Unmet needs in special services/rehabilitation and education were also rated important by families and were the most common unmet needs for children. The majority of our sample had important financial difficulties and low household income. Nevertheless, similar to previous studies,\textsuperscript{16} special service/rehabilitation and educational needs were rated as more important than financial needs by the families. For the vast majority of children in our study, these needs were unmet. The MetabERN study reported on the discontinuation of intervention services like speech therapy and physiotherapy for 42% of the patient organizations.\textsuperscript{12} A study from Brazil (included 1466 patients with rare diseases) reported that for 68% of children, rehabilitation sessions had been cancelled.\textsuperscript{24} Both studies included adults as well as children. The even higher unmet needs in our study (78% or higher depending on service type) may be explained by a number of factors including the greater needs of children compared to adults, the deficiencies in the system for preparing tele-interventions,\textsuperscript{29} and contextual reasons for lower demand for interventions from the families. There are no other studies reporting on the educational needs of children with RIMDs to compare our results. Less than 1 in 10 school-aged children were able to attend school via tele-schooling which had been made available for all Turkish children through televised classroom system developed by the Ministry of Education. The reasons for not attending such schooling were given by the families as scarce programs for children with developmental difficulties. In crises such as the pandemic, educational systems must be prepared to meet the needs of children with special needs including RIMDs.

Social service needs including government-paid financial supports and tax reductions were met due to the centralized and digitalized system of paying such social supports to children with disabilities in the Turkish system.

We had hypothesized that child-related factors such as being younger than 3 years would be associated with more unmet needs in health care as this period needs close management of developmental difficulties and health concerns. We have also thought that family-related factors such as educational or financial status or COVID-19-related factors such as having illness in the family would be related to unmet needs. However, there were no such associations. Children who had significant developmental delays and/or disabilities were more likely to have unmet healthcare needs. There have been no prior studies during the pandemic that have examined the associations between child, family, and environmental factors and unmet health care needs for children with RIMDs.

The main strength of this study is that it uses a bioecological comprehensive framework for examining unmet needs. The cross-sectional design precludes drawing causal associations in our study, but with our large and diverse sample, we were able to examine associations between child, family, and environmental characteristics and unmet needs. Our main limitation is that we have used a single-center referred sample which may jeopardize generalizability. Nevertheless, the children came from many diverse areas of the country to our tertiary center.

The results of this study have demonstrated that children with RIMDs and their families have important and specific unmet needs during COVID-19 pandemic. Our findings imply that there is a need for action by clinicians, researchers, and policy makers to explore and address the unmet needs of children with RIMDs and their families especially who has significant developmental delays and/or disabilities during COVID-19 pandemic and possible future crises.

| Table 3. Unmet Needs During the COVID-19 Pandemic |
|-----------------------------------------------|
| Domains of Services                            | Met Needs Before Pandemic (N = 229) | Unmet Needs During Pandemic* |
|                                               | n   | %    | n   | %    |
| Health care needs                             |     |      |     |      |
| Access to health care for follow-up           | 229 | 100.0| 110 | 48.0 |
| Receiving medicine and/or enzyme prescriptions| 178 | 77.7 | 113 | 63.5 |
| Support for specific diet                     | 84  | 36.7 | 51  | 60.7 |
| Educational needs                             |     |      |     |      |
| Preschool education (n = 97)                  | 28  | 28.8 | 26  | 92.3 |
| Schooling (n = 84)                            | 77  | 91.7 | 74  | 96.1 |
| Special services and rehabilitation needs     |     |      |     |      |
| Special education for cognitive difficulties  | 84  | 36.7 | 79  | 94.0 |
| Physiotherapy                                 | 59  | 25.8 | 51  | 86.4 |
| Speech and language therapy                   | 32  | 14.0 | 25  | 78.1 |
| Vision/hearing rehabilitation                | 5   | 2.2  | 5   | 100.0|
| Occupational therapy                          | 2   | 0.8  | 2   | 100.0|

*Unmet needs during pandemic column was calculated by dividing the number (n) of unmet needs during the pandemic to the number (N) of met needs before the pandemic.
### Table 4. Bivariate and Multivariable Analyses of Child-, Family-, and Environment-Related Factors Associated with the Unmet Health Care Needs

| Proportions (N = 229) | Unmet Health Care Needs Present |  |  |  |
|-----------------------|---------------------------------|---|---|---|
|                       | n     | %    | n     | %*  | OR   | 95% CI  | P  |
| **Bivariate analyses**|       |      |       |     |      |         |   |
| **Child-related factors**|       |      |       |     |      |         |   |
| Sex                   |       |      |       |     |      |         |   |
| Girls                | 105   | 45.9 | 79    | 75.2| 1.24 | 0.69-2.40| .469|
| Boys                 | 124   | 54.1 | 88    | 71.0|      |         |   |
| Age                  |       |      |       |     |      |         |   |
| ≤3 years             | 82    | 35.8 | 62    | 75.6| 1.24 | 0.67-2.30| .495|
| >3 years             | 147   | 64.2 | 105   | 71.4|      |         |   |
| Diet-dependent metabolic disorder |       |      |       |     |      |         |   |
| Present              | 84    | 36.7 | 62    | 73.8| 1.07 | 0.59-2.00| .819|
| Absent               | 145   | 63.3 | 105   | 72.4|      |         |   |
| Developmental delay  |       |      |       |     |      |         |   |
| Present              | 184   | 80.3 | 142   | 77.2| 2.71 | 1.37-5.35| .003|
| Absent               | 45    | 19.7 | 25    | 55.6|      |         |   |
| **Environmental/contextual factors**|       |      |       |     |      |         |   |
| Nuclear family        |       |      |       |     |      |         |   |
| Present              | 190   | 83.0 | 138   | 72.6| 0.92 | 0.42-2.00| .825|
| Absent               | 39    | 17.0 | 29    | 74.4|      |         |   |
| Residing outside Ankara|       |      |       |     |      |         |   |
| Present              | 103   | 45.0 | 81    | 78.6| 1.71 | 0.94-3.13| .078|
| Absent               | 126   | 55.0 | 86    | 68.3|      |         |   |
| Mother reporting depression |       |      |       |     |      |         |   |
| Present              | 67    | 29.3 | 54    | 80.6| 1.80 | 0.90-3.60| .093|
| Absent               | 162   | 70.7 | 113   | 68.9|      |         |   |
| Income level         |       |      |       |     |      |         |   |
| ≤Minimum wage        | 126   | 55.0 | 90    | 71.4| 0.84 | 0.47-1.52| .573|
| >Minimum wage        | 103   | 45.0 | 77    | 74.8|      |         |   |
| Loss of job in the household |       |      |       |     |      |         |   |
| Present              | 58    | 25.3 | 42    | 72.4| 0.97 | 0.50-1.88| .919|
| Absent               | 171   | 74.7 | 125   | 73.1|      |         |   |
| Decrease in monthly household income |       |      |       |     |      |         |   |
| Present              | 100   | 43.7 | 78    | 78.0| 1.59 | 0.87-2.91| .128|
| Absent               | 129   | 56.3 | 89    | 69.0|      |         |   |
| Change in primary caregiver |       |      |       |     |      |         |   |
| Present              | 28    | 12.2 | 22    | 78.6| 1.42 | 0.55-3.68| .473|
| Absent               | 201   | 87.8 | 145   | 71.2|      |         |   |
| Paternal education   |       |      |       |     |      |         |   |
| <High school         | 182   | 79.5 | 135   | 55.5| 1.35 | 0.67-2.71| .402|
| ≥High school         | 47    | 20.5 | 32    | 48.9|      |         |   |
| Maternal education   |       |      |       |     |      |         |   |
| <High school         | 131   | 57.2 | 94    | 71.8| 0.87 | 0.48-1.58| .645|
| ≥High school         | 98    | 42.8 | 73    | 74.5|      |         |   |
| COVID-19 in the family members |       |      |       |     |      |         |   |
| Present              | 43    | 18.8 | 32    | 74.4| 1.10 | 0.52-2.34| .807|
| Absent               | 186   | 81.2 | 135   | 72.6|      |         |   |
| **Multivariable logistic regression analysis**|       |      |       |     |      |         |   |
| Developmental delay  |       |      |       |     | 2.31 | 1.14-4.67| .020|
| Residing outside Ankara|       |      |       |     | 1.56 | 0.84-2.93| .160|
| Mother reporting depression |       |      |       |     | 1.72 | 0.84-3.85| .188|
| Decrease in monthly household income |       |      |       |     | 1.48 | 0.80-2.75| .216|

OR, odds ratio; COVID-19, coronavirus disease 2019.
P values represent bivariate chi-square and multivariable logistic regression tests.
Nagelkerke $R^2 = 0.083$, Hosmer and Lemeshow value = 0.671.
*% in unmet health care needs present column was calculated by dividing the number (n) of unmet needs by the number of sub-variables, such as girls, boys, etc., provided in the table.

**Ethics Committee Approval**: This study was approved by the Ethics Committee of Ankara University (Approval No: 18-483-20).

**Informed Consent**: Verbal informed consent was obtained from all participants who participated in this study.

**Peer-review**: Externally peer-reviewed.

**Author Contributions**: Concept – E.O.A., F.T.E.; Design – E.O.A., F.T.E.; Supervision – E.O.A, F.T.E.; Materials – E.O.A., N.D., M.K.Y., U.O., F.A., G.H.; Data Collection and/or Processing – E.O.A., N.D., M.K.Y., U.O., F.A., G.H.; Analysis and/or Interpretation – E.O.A., N.D., M.K.Y., U.O., F.A., G.H.; Literature Review – E.O.A.; Writing – E.O.A., N.D., M.K.Y., U.O., F.A., G.H.; Critical Review – F.T.E.

**Acknowledgments**: The authors thank Professor Ilgın Ertem for her invaluable comments on the manuscript. Also, the authors are grateful to children and their families for their contribution to this study.

**Declaration of Interests**: The authors have no conflict of interest to declare.
Funding: The authors declared that this study has received no financial support.

REFERENCES

1. Ghosh A, Schlecht H, Heptinstall LE, et al. Diagnosing childhood-onset inborn errors of metabolism by next-generation sequencing. Arch Dis Child. 2017;102(11):1019–1029. [CrossRef]

2. Ullah MA, Husseni AM, Mahmood SU. Consanguineous marriages and their detrimental outcomes in Pakistan: an urgent need for appropriate measures. Int J Commun Med Public Health. 2017;5(1):3. [CrossRef]

3. Hazan G, Hershkovitz E, Staretz-Chacham O. Incidence of inherited metabolic disorders in southern Israel: a comparison between consanguinity and non-consanguinity communities. Orphanet J Rare Dis. 2020;15(1):331. [CrossRef]

4. Mayer ML, Skinner AC, Slifkin RT. Unmet need for routine and specialty care: data from the National Survey of Children with Special Health Care Needs. Pediatrics. 2004;113(2):e109–e115. [CrossRef]

5. Newacheck PW, Hughes DC, Hung YY, Wong S, Stoddard JJ. The impact of COVID-19 on rare metabolic patients and healthcare providers: results from two MetaBern surveys. Orphanet J Rare Dis. 2020;15(1):341. [CrossRef]

6. Saudubray JM, Garcia-Cazorla À. Inborn errors of metabolism overview: pathophysiology, manifestations, evaluation, and management. Pediatr Clin North Am. 2018;65(2):179–208. [CrossRef]

7. Martins AM, Pessoa ALS, Quesada AA, Ribeiro EM. Unmet needs in PKU and the disease impact on the day-to-day lives in Brazil: results from a survey with 228 patients and their caregivers. Mol Genet Metab Rep. 2020;24:100624. [CrossRef]

8. Porter KA, O’Neill C, Drake E, et al. Parent experiences of Sanfilippo syndrome impact and unmet treatment needs: a qualitative assessment. Neurol Ther. 2021;10(1):197–212. [CrossRef]

9. Pelentsov LJ, Fielder AL, Laws TA, Esterman AJ. The supportive care needs of parents with a child with a rare disease: results of an online survey. BMCFamPract. 2016;17:88. [CrossRef]

10. Lampe C, Dionisi-Vici C, Belllettato CM, et al. The impact of COVID-19 on rare metabolic patients and healthcare providers: results from two MetaBern surveys. Orphanet J Rare Dis. 2020;15(1):341. [CrossRef]

11. Rare Diseases Europe. Available at: https://www.eurordis.org/content/people-living-rare-disease-were-severely-impacted-during-first-covid-19-wave-30-million-people-europe-must-not-forget Accessed August 10, 2021.

12. Chung CCY, Ng YNC, Jain R, Chung BHY. A thematic study: impact of COVID-19 pandemic on rare disease organizations and patients across ten jurisdictions in the Asia Pacific region. Orphanet J Rare Dis. 2021;16(1):119. [CrossRef]

13. Elmonem MA, Belanger-Quintana A, Bordugo A, et al. The impact of COVID-19 pandemic on the diagnosis and management of inborn errors of metabolism: a global perspective. Mol Genet Metab. 2020;131(3):285–288. [CrossRef]

14. Oge Enver E, Hopucruoglu D, Ahmadzada S, Zubarioglu T, Aktuglu Zeybek AC, Kiyikm E. Challenges of following patients with inherited metabolic diseases during the COVID-19 outbreak. A cross-sectional online survey study. J Pediatr Endocrinol Metab. 2021;34(1):103–107. [CrossRef]

15. Kahraman AB, Yildiz Y, Çiki K, et al. Invisible burden of COVID-19: enzyme replacement therapy disruptions. J Pediatr Endocrinol Metab. 2021;34(5):539–545. [CrossRef]

16. Global Research on Developmental Disabilities Collaborators. Developmental disabilities among children younger than 5 years in 195 countries and territories, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Glob Health. 2018;6(10):e1100–e1121. [CrossRef]

17. UN General Assembly. Convention on the Rights of the Child, 20 November 1989, United Nations, Treaty Series; 1989:3. Available at: https://www.refworld.org/docid/3ae6b38f0.html. Accessed June 18, 2021.

18. Hacettepe University Institute of Population Studies. 2018 Turkey Demographic and Health Survey. Ankara, Turkey: Hacettepe University Institute of Population Studies, T.R. Presidency of Turkey Directorate of Strategy and Budget and TÜBİTAK, 2018.

19. Özalp Akın E, Mustafayev R, Pekcici EBB, Ertem I. Applicability of a tool for comprehensive pediatric assessments: the expanded Guide for monitoring child development. J Pediatr Congenit Dis. 2021;7(1):107. [CrossRef]

20. Bingolter Pekcici EB, Özalp Akın E, Ayrançı Sukaci I, et al. Addressing early childhood development and developmental difficulties in Turkey: a training programme for developmental pediatrics units. Arch Argent Pediatr. 2020;118(4):e384–e391. [CrossRef]

21. Bronfenbrenner U, Ceci S. Nature-nurture reconceptualized in developmental perspective: a bioecological model. Psychol Rev. 1994;101(4):568–586. [CrossRef].

22. Rare Disease Ireland. Living with a Rare Disease in Ireland during the COVID-19 pandemic 2020. https://rdi.ie/wp-content/uploads/2020/05/Research-Report-Living-with-a-rare-disease-in-Ireland-during-the-COVID-19-pandemic.pdf Accessed July 10, 2021.

23. Yildiz Y, Sivri HS. Difficulties associated with enzyme replacement therapy for mucopolysaccharidoses. Turk Arch Pediatr. 2021;56(6):602–609. [CrossRef]

24. Shur N, Atabaki SM, Kisling MS, et al. Rapid deployment of a telemedicine care model for genetics and metabolism during COVID-19. Am J Med Genet A. 2021;185(1):68–72. [CrossRef]

25. Brunetti-Pierri N, Fecarotta S, Staiano A, Strisciuglio P, Parenti G. Ensuring continuity of care for children with inherited metabolic diseases at the time of COVID-19: the experience of a metabolic unit in Italy. Genet Med. 2020;22(7):1178–1180. [CrossRef]

26. Schwartz IVD, Randon DN, Monsores N, et al. SARS-CoV-2 pandemic in the Brazilian community of rare diseases: a patient reported survey [published online ahead of print, 2021 Jan 20]. Am J Med Genet C Semin Med Genet. 2021;187(3):301–311. [CrossRef]

27. Zubarioglu T, Hopucruoglu D, Uygun E, et al. The impact of telemedicine for monitoring and treatment of phenylketonuria patients on metabolic outcome during coronavirus disease-19 outbreak [published online ahead of print, 2021 Mar 12]. Telemed J E Health. 2022;28(2):258–265. [CrossRef]

28. Aydemir S, Ocak S, Saygılı S, et al. Telemedicine applications in a tertiary pediatric hospital in Turkey during COVID-19 pandemic [published online ahead of print, 2020 Dec 9]. Telemed J E Health. 2021;27(10):1180–1187. [CrossRef]

29. Hoffer-Hawlik MA, Moran AE, Burka D, et al. Leveraging telemedicine for chronic disease management in low- and middle-income countries during Covid-19. Glob Heart. 2020;15(1):63. [CrossRef]