Developmental Risk Factors of Young Children with Inherited Metabolic Disorders During the COVID-19 Pandemic

Erken Çocukluk Döneminde Kalıtsal Metabolik Hastalığı Olan Çocukların COVİD-19 Pandemisinde Gelişimsel Risk Etmenleri

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ABSTRACT

Objective: Coronavirus disease 2019 (COVID-19) pandemic has led to emergence of new developmental risk factors. Developmental risk factors for young children with inherited metabolic disorders have not been studied based on a comprehensive framework. We aimed to determine the developmental risk factors of young children with inherited metabolic disorders during COVID-19 pandemic based on bioecological theory.

Material and Methods: In a cross-sectional design, children aged 0-42 months that who had appointments at Ankara University School of Medicine Department of Pediatrics (AUDP) Pediatric Metabolism Division with the diagnoses of inherited metabolic disorders were recruited between October 1st, 2020 to January 1st, 2021. Developmental risk factors were assessed with a semi-structured interview based on questions of the Expanded Guide for Monitoring Child Development revised for the pandemic at AUDP Developmental Pediatrics Division.

Results: The sample consisted of 95 children with inherited metabolic disorders (median age:25, IQR: 17-35 months, 57.9% boys). Most children (54 children, 56.8%) had amino-acid metabolism disorders. Child-related developmental risk factors included new behavioral problems in most of the sample (53 children, 55.8%) and increased screen time in 26 children (27.3%). As family-related developmental risk factors, 40 children (42.1%) were living with a family member diagnosed with major depression. In environment-related developmental risk factors; 41 families (43.2%) experienced a decrease in their household income and 21 (22.1%) loss of job during the pandemic, 17 (17.9%) delay in health care follow up visits, 8 of 28 (28.6%) discontinuity of intervention and rehabilitation services. Participation in life was severely limited in 42 (44.2%) children with inherited metabolic disorders.

Conclusion: Apart from life threatening medical problems, children and their families in Turkey and potentially in other low- and middle-income countries face multiple developmental risk factors. Preventable or reducible risk factors should be addressed to support these children's development in this pandemic and beyond.

Key Words: Child Development, COVID-19, Family, Inborn Errors of Metabolism, Risk Factors

ÖZ

Amaç: Koronavirus hastalığı 2019 (COVİD-19) pandemisi, yeni gelişimsel risk faktörlerinin ortaya çıkmasına neden olmuştur. Ancak kalıtsal metabolik hastalıkları olan küçük çocuklar için gelişimsel risk faktörleri, kapsamlı bir çerçeveye dayalı olarak çalışılmamıştır. Bu araştırmanın amacı COVİD-19 pandemisinde kalıtsal metabolik hastalığı olan küçük çocukların biyoekolojik kuram çerçevesinde gelişimsel risk etmenlerini belirlemektir.

Gereç ve Yöntemler: Kesitsel desendeki araştırmada, Ankara Üniversitesi Tıp Fakültesi, Çocuk Sağlığı ve Hastalıkları Anabilim Dalı (AUÇH) Çocuk Metabolizma Bilim Dalında kalıtsal metabolik hastalık tanısı ile randevusu olan 0-42 aylık

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Ethics Committee Approval / *Etik Kurul Onayı*: This study was conducted in accordance with the Helsinki Declaration Principles. The study was approved by the Ethics Committee of the Ankara University School of Medicine (Decision number: İ8-484-20, 10.09.2020).

Contribution of the Authors / Yazarların katkısı*: *OZALP AKIN E: Constructing the hypothesis or idea of research and/or article, Planning methodology to reach the Conclusions, Organizing, supervising the course of progress and taking the responsibility of the research/study, Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments, Taking responsibility in logical interpretation and conclusion of the results, Taking responsibility in necessary literature review for the study, Taking responsibility in the writing of the whole or important parts of the study, Reviewing the article before submission scientifically besides spelling and grammar. ***EMINOGLU FT:*** Constructing the hypothesis or idea of research and/or article, Organizing, supervising the course of progress and taking the responsibility of the research/study, Taking responsibility in logical interpretation and conclusion of the results, Reviewing the article before submission scientifically besides spelling and grammar.

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çocuklar, 1 Ekim 2020-1 Ocak 2021 tarihleri arasında çalışmaya alındı ve AUÇH Gelişimsel Pediatri Bilim Dalında Genişletilmiş Gelişimi İzlenme ve Destekleme Rehberi'nin sorularına dayalı olarak yarı yapılandırılmış bir görüşme ile gelişimsel risk etmenleri değerlendirildi.

Bulgular: Örneklem, kalıtsal metabolik bozukluğu olan 95 çocuktan oluşmaktadır (ortanca yaş: 25, ÇAA: 17-35 ay, %57.9 erkek). Çocukların çoğunda (54 çocuk, %56.8) aminoasit metabolizma bozukluğu tanısı bulunmaktaydı. Çocukla ilgili gelişimsel risk etmenleri alanında örneklemin çoğunda (53 çocuk, %55.8) yeni ortaya çıkan davranış sorunları ve 26 çocukta (%27.3) artmış ekran süresi saptandı. Aile ile ilgili gelişimsel risk etmenleri olarak, 40 çocuğun (%42.1) evinde majör depresyon tanısı almış bir birey bulunmaktaydı. Çevre ile ilgili gelişimsel risk etmenleri alanında 41 aile (%43.2) pandemide hane gelirinde azalma, 21 aile (%22.1) iş kaybı, 17 aile (%17.9) sağlık izlemlerinde gecikme, girişim ve rehabilitasyon hizmetleri alan 28 ailenin 8'i (%28.6) kesinti bildirdi, 42 (%44.2) çocuğun yaşama katılımı ciddi şekilde sınırlıydı.

Sonuç: Türkiye'de ve büyük olasılıkla diğer düşük ve orta gelirli ülkelerde kalıtsal metabolik hastalığı olan çocuklar yaşamı tehdit eden tıbbi sorunların yanı sıra birden fazla çevresel gelişimsel risk etmeni ile karşı karşıyadır. Bu çocukların pandemi ve diğer olası kriz dönemlerinde gelişimlerini desteklemek için önlenebilir risk etmenleri önlenmeli ve mümkün olduğunca risk etmenleri azaltılmalıdır.

Anahtar Sözcükler: Gelişim, COVİD-19, Aile, Kalıtsal Metabolik Hastalıklar, Risk Etmenleri

INTRODUCTION

During Coronavirus disease 2019 (COVID-19) pandemic, considerable strain on daily life of children with inherited metabolic disorders and their families has led to emergence of new developmental risk factors (1,2). Knowledge of the developmental risk factors of children with inherited metabolic disorders is crucial as the management of developmental difficulties in young children cannot be accomplished without information on risk factors.

Developmental risk factors are the factors that may affect the child, the child's proximal or distal environment and have a negative influence on child development. These factors may be biomedical, psychosocial or both together (3). Children with inherited metabolic disorders have well known and mostly severe biomedical risk factors that affect development in developmental domains including cognitive, language, motor and social-emotional development. These biomedical risk factors arise from complex and chronic health care problems that may include almost all organ systems such as cardiac, pulmonary, renal, hepatic, endocrine, central and peripheric nervous system and may cause failure to thrive, developmental difficulties and disabilities (4-7). Children with inherited metabolic disorders need close health care follow up by specialized teams, specific diet according to their disease, ongoing management of specific treatments and metabolic destabilizations that gained more importance in the COVID-19 pandemic (2,8).

In low and middle income counties (LMICs) many children younger than 5 years are exposed to complex interaction of biomedical and psychosocial multiple risk factors, which detrimentally affect their cognitive, motor, and social-emotional development (9). It was reported that children with inherited metabolic disorders may have important psychosocial risk factors such as poverty, unstimulating home environments, lack of social support, stigmatization, and limited participation in life that pose additional serious risks for their development. The pandemic brought new risk factors (10). Even in high income countries more than half of the families of children with inherited metabolic diseases reported the need for including food and financial assistance, and childcare support during COVID-19 pandemics as well as access to medical care (2,11).

According to Bronfenbrenner's bioecological theory development of a child happens through the complex and dynamic interactions among the child's health conditions, temperament, developmental strengths and difficulties; the relationships and interactions with and within the family including closest caregivers, siblings, as well as proximal caregiving environment and distal environment such as living and working conditions, health and social services, physical environment, education and intervention services (12). Therefore, the developmental risk factors that affect a child development may be related to the child, proximal caregiving environment (family) and distal environment. Although COVID-19 pandemic had an enormous effect on children with inherited metabolic disorders, developmental risk factors for youngest children with inherited metabolic disorders who have the most potential to reach their optimal development with interventions have not been studied based on a comprehensive framework.

In this study, we aimed to determine the developmental risk factors of young children with inherited metabolic disorders during COVID-19 pandemic based on bioecological theory.

METARIAL and METHODS

In a cross-sectional design, children aged 0-42 months that who had appointments at Ankara University School of Medicine Department of Pediatrics (AUDP), Pediatric Metabolism Division with the diagnoses of inherited metabolic disorders were recruited in three-months period between October 1st, 2020 and January 1st, 2021. Children were included if they were able to come to the hospital during the study period and their parents provided informed consent to participate in the study. The study was approved by the Ethics Committee of the Ankara University School of Medicine (Decision number: İ8-484-20, 10.09.2020).

The assessment of developmental risk factors of children with inherited metabolic disorders was conducted at AUDP,

Developmental Pediatrics Division. All children with inherited metabolic disorders have appointments in the Developmental Pediatrics outpatient clinic at the day of their appointments in Pediatric Metabolism outpatient clinic as per routine patient follow up procedures. In the Developmental Pediatrics outpatient clinic, after asking for informed consent for the study, a semi-structured interview lasting approximately 20 minutes was conducted with the parents who provided their consent using questions of the Expanded Guide for Monitoring Child Development (Expanded GMCD) (13). Sociodemographic data was also retrieved from the Expanded GMCD. Information related to the health conditions of the child such as the diagnoses, medications, and specific diet requirements and developmental conditions including delays, disabilities and related disability reports were determined from the hospital records.

The Expanded GMCD is a written questionnaire based on the World Health Organization International Classification of Functioning, Disability and Health (ICF) and Nurturing Care frameworks (13). The Expanded GMCD provides information on health conditions, developmental functioning, activities and participation, as well as the environmental factors including developmental risk factors. A previous study has shown that the open-ended questions of the Expanded GMCD were accepted and responded by the families of children with inherited metabolic disorders (14).

Developmental risk factors were conceptualized on the bioecological theory and included child, family and environment related factors. Child related developmental risk factors included having diet dependent metabolic disorders, need for hospitalization during the pandemic, COVID-19 infection in the child, any regression stated by the families in language, motor, cognitive or social-emotional domains due to pandemic related conditions (not due to metabolic decompansations, examples include seize of special education and/or rehabilitation services, difficulties in caregiving environment etc.), existence of sleep, eating/feeding and other behavioral problems (such as stubbornness, frequent meltdowns, excessive crying etc.) and increased screen time during the COVID-19 pandemic. Family related developmental risk factors included low maternal and paternal education defined as ≤5 years, change of primary caregiver in the pandemic, increased maternal fatigue, mother spending less daily time with her child than the pre-pandemic period, mother or father having treatment for major depression as well as diagnosis of depression in other household members, COVID-19 infection and COVID-19 related death in the household members. Environment related developmental risk factors included decrease in monthly household income compared to pre-pandemic period, loss of job in the household members, and discontinuation to health care follow up, intervention and rehabilitation services due to pandemic related conditions (such as quarantine periods or fear of infection). Therefore, we have added pandemic-related developmental risk factor questions to the "Developmental functioning", "Activities and participation in life" and "Environmental factors" sections of the Expanded GMCD for the purpose of this study. These were asked as structured questions and coded as "present" or "absent." During the assessment these questions were read to the parents and the answers were recorded by the developmental pediatrician. The presence of another child and/or family-environment related developmental risk factor in the interview was also recorded. Reported developmental risk factors were addressed when possible and developmental support was provided at the developmental pediatrics outpatient clinic.

Sociodemographic data included age, gender, number and age of siblings, maternal and paternal age and education, monthly household income, number of family members living together, the city that the family lives as well as whether the child lives in a nuclear or an extended family.

Data analyses

Descriptive statistics were used as frequencies for categorical data; means and standard deviations for normal continuous distributions; and medians and interquartile ranges (IQR) otherwise. The Shapiro-Wilk test was used to check whether there was a normal distribution of the numerical variables. Statistical analyses were done using IBM SPSS 20.0 (SPSS Inc., Chicago, IL, USA) package program.

RESULTS

A total of 98 young children younger than 42 months with inherited metabolic disorders who were seen at AUDP, Pediatric Metabolism Division in the study period were considered for eligibility for this study. Of these 3 did not provide consent for the study and the sample consisted of 95 children with inherited metabolic disorders.

Sociodemographic and health related characteristics of the sample

The sociodemographic characteristic of the sample are shown in Table I. The median age of the sample was 25, IQR: 17-35 months, 55 children were boys (57.9%). Median maternal and paternal ages were 30.0 (IQR: 25-35) and 33.0 (IQR: 29-38) years. Most of the children had at least one sibling and 47 (49.5%) children were born to parents with consanguinity. Most of the children were residing in Ankara, the capital of Turkey. Most mothers 89 were homemakers (93.7%) whereas 85 fathers (89.5%) were working on a job.

The diagnoses of the children were as following: 54 children (56.8%) had amino acid metabolism disorders (29 had biotinidase deficiency, 10 hyperphenylalaninemia, 9 organic acidemia, 4 phenylketonuria, 1 tyrosinemia, 1 cystinuria), 15(16.7%) mitochondrial disorders, 7(7.4%) lysosomal and

Table I: Sociodemographic characteristics and diagnoses (n=95).

Characteristics of children	n (%)
Boys	55 (57.9)
Girls	40 (42.1)
Age (months)	
0-12	15 (15.8)
13-24	30 (31.6)
25-42	50 (52.6)
Maternal education	
Never went to school	4 (4.2)
Primary school	18 (18.9)
Secondary school	29 (30.5)
High school graduate	26 (27.4)
University education or higher	18 (18.9)
Paternal education	
Never went to school	1 (1.1)
Primary school	19 (20.0)
Secondary school	18 (18.9)
High school graduate	34 (54.7)
University education or higher	23 (24.2)
Number of siblings	
Only child	35 (36.8)
One sibling	30 (31.6)
≥2 siblings	30 (31.6)
Nuclear family	75 (78.9)
Residing in Ankara	58 (61.1)

peroxisomal disorders, 4(4.2%) carbohydrate metabolism disorders, 3 (3.2%) congenital glycosylation disorders, 1 (1.1%) fatty acid oxidation disorder, 1 (1.1%) urea cycle disorder, and 10 (10.5%) other metabolic disorders. Most of the children (67.4%) had developmental delay in at least one domain of development, 33 (34.7%) had disability benefits report and 7 (7.4%) used orthoses.

Developmental risk factors in the COVID-19 pandemic

The developmental risk factors conceptulized on bioecological theory as child-related and family/environment-related developmental risk factors are summarized in Table 2. All of the sample had at least one child related developmental risk factor due to their metabolic disease, most (69 children, 72.6%) had two, 46 (48.4%) children had ≥3 child -related developmental risk factors. Most of the sample 52 (54.7%) had ≥3 family and/or environment related developmental risk factors; 84 children, (88.4%) had at least one, 77 (81.1%) had two family and/or environment related developmental risk factors. When child and family and/or environment related developmental risk factors are considered 31 (32.6%) children had ≥6 developmental risk factors.

Child-related developmental risk factors. When the families were asked about the traejctory of their child's development including in language, motor, cognitive or social-emotional development domains; 7 families (7.4%) reported that their child regressed in developmental functioning in at least one

Table II. Developmental risk factors of the sample.

Child related developmental risk factors	n (%)
Biomedical risk factors	
Having a diet dependent metabolic disease	23 (24.2)
Hospitalization during the pandemic	17 (17.9)
COVID-19 infection in the child	0 (0.0)
Existence of behavioral problems during the pandemic	
Sleep difficulties	20 (21.1)
Difficult behavior such as meltdowns, excessive crying etc.	19 (20.0)
Eating and/or feeding difficulties	14 (14.7)
Increased screen time	26 (27.3)
Regression in development in at least one developmental domain	6 (6.3)
Family related developmental risk factors	
Maternal education ≤ 5 years	22 (23.2)
Paternal education ≤ 5 years	20 (21.1)
Increase in maternal fatigue	34 (35.8)
COVID-19 infection in the family members	23 (25.0)
Diagnosis of depression in the family	
Maternal depression	15 (15.8)
Paternal depression	7 (7.4)
Depression in other household members	18 (18.9)
Change of primary caregiver during the pandemic	14 (14.7)
Mother spending less daily time with her child than usual	5 (5.3)
Death due to COVID-19 in the family members	0 (0.0)
Environment related developmental risk factors	
Decrease in monthly household income	41 (43.2)
Loss of job in the household members	21 (22.1)
Delay in their health care follow up visits	17 (17.9)
Discontinuity of intervention and rehabilitation services (n=28)	8 (28.6)
Getting out from home for leisure activities/ visiting relatives etc. ≤once a week	56 (58.9)

domain since the beginnig of the pandemic. The reasons provided by the parents included discontnuity to rehabilitation services in 3 families, family members' COVID-19 infection in 2, and depression in caregivers in 2 families. Most of the families (55.8%) reported a behavioral problem in their child that existed during the pandemic including eating/feeding, sleep or other daily behaviors. Almost one third of the children (32.6%) had experienced eating/feeding difficulty in the pandemic including 14 (14.7%) undereating and 17 (17.9%) overeating when compared to pre-pandemic period. Sleep schedule and duration has not changed significantly for most of the children (68.4%) according to families, while in 20 (21.1%) children the family reported exitence of sleep problems.

Family related developmental risk factors. Almost one fifth of the sample maternal (23.2%) and paternal (21.1%) education was ≤ 5 years. Seventy (73.7%) families stated that the time that the mother spent with her child to support development (like playing, reading, talking during daily activities) did not change and 20 (21.1%) spent more time than usual. Fourty children

(42.1%) were living with a family member diagnosed with major depression.

Environment related developmental risk factors. Most families' income (53.5%) was less than minimum wage and almost one fifth (22.1%) of the families experienced a loss of job during the pandemic. Loss of job involved fathers in 17 families, other household members such as uncle or grandfather in 2 families and one family experienced loss of job in both the mother and the father. In the participation in life domain, when the families were asked about the frequency of getting out from their home with their child for leisure activities, going to parks or visiting friends/relatives etc.; 42 (44.2%) children did not have a regular outside activity per week, 14 children (14.7%) were getting out home for one of these activities once a week, 17 children (17.9%) 2-3 times a week and 22 children (23.2%) ≥4 times a week.

DISCUSSIONS

This study demonstrated the developmental risk factors of young children with inherited metabolic disorders during COVID-19 pandemic from a middle-income country, Turkey. Many developmental risk factors arised during the COVID-19 pandemic. All young children had at least one, one third of the sample had six or more developmental risk factors based on bioecological theory. These findings draw attention to addressing the preventable risk factors that the children with inherited metabolic disorders carry during crises periods like a pandemic and imply for clinicians and policy makers in the COVID-19 pandemic and beyond.

There have been studies including the developmental risk factors of children with inherited metabolic disorders while our study is the first study investigating the developmental risk factors based on bioecological framework for youngest children with inherited metabolic disorders. Almost one third of the sample had a cumulation of six or more child and family/ environment related risk factors. Historically, the cumulation of biomedical and psychosocial risk factors has been referred as "double jeopardy" to describe the detrimental effect of poverty on child development (15).

In our study as child related developmental risk factors; all children had metabolic disorders and most had known developmental delays. More than half of the families reported behavioral problems and one fourth increased screen time parallel to studies showing increased behavioral difficulties in young children with specific health care needs during the COVID-19 pandemic (16). Additional to these risk factors, most common family and/or environment related risk factors were low maternal and paternal education, depression in family members, financial difficulties, limited participation in life. Oge Enver et al. reported difficulties for children with inherited metabolic disorders (mean age was 7, higher than our study) from Turkey in the COVID-19 pandemic. The results included financial difficulties in most of the sample as an environmental developmental risk factor which was also evident in our study (17). A recent qualitative study from Canada highlighted the experiences of families of children with inherited metabolic disorders and it was reported that participation in social life was one of the themes that arised in the interviews (18). Another important environmental risk factor was discontinuity to health care and intervention and/or rehabilitation services due to quarantines and fear of COVID infection which was evident in many countries around the world (2,11). Evidence shows that timely interventions addressing developmental risk factors such as poverty, maternal depression, low maternal education, restricted learning opportunities and inequities can improve early childhood development especially in low and middle countries (19,20). At AUDP the clinicians from Pediatric Metabolism Division reached the children and their families via telehealth during the pandemic, provided support in information, answered the questions of the family. System related difficulties were suspended with efforts of the clinicians. Additionally, AUDP Developmental Pediatrics Division provided early intervention with Guide for Monitoring Child Development (GMCD) early intervention package with telehealth (21-23). These may be protective for these vulnerable children and their families during crises. There is need for research on child and family related protective factors and resilience for young children with inherited metabolic disorders during crises.

Our study has some limitations. The cross-sectional design precludes drawing casual associations. We have provided the number of risk factors but we don't know the effect size of risk factors and the relationship between different risk factors (such as financial difficulties may cause depression). Our small sample size is relatively large while the sample was heterogenic in terms of diagnosis and included both severe (such as urea cycle disorders) and less severe metabolic diseases (such as hyperphenylalaninemia). The major strength of this study is the conceptual framework based on the bioecological theory.

The implications of our study are important for the care of children with metabolic disorders in this pandemic and other crises periods. Our results indicate that apart from life threatening medical problems, children and their families in Turkey and potentially in other low- and middle-income countries face multiple child, family and environment related developmental risk factors that puts further burden in their developmental trajectory. Preventable or reducible risk factors such as inappropriate caregiving environment, depression, financial difficulties, continuum of care in health and intervention services should be addressed by multisectoral coverage.

REFERENCES

1. World Health Organization. Coronavirus disease 2019 (COVID-19) Situation Report-51. 2020; 11/02/2021.

2. Lampe C, Dionisi-Vici C, Bellettato CM, Paneghetti L, van Lingen C, Bond S, et al. The impact of COVID-19 on rare metabolic patients and healthcare providers: results from two MetabERN surveys. Orphanet J Rare Dis 2020;15:341.
3. Walker SP, Wachs TD, Gardner JM, Lozoff B, Wasserman GA, Pollitt E, et al. Child development: risk factors for adverse outcomes in developing countries. Lancet 2007;369:145- 57.
4. Ramsay J, Morton J, Norris M, Kanungo S. Organic acid disorders. Ann Transl Med 2018;6:472.
5. Wasim M, Awan FR, Khan HN, Tawab A, Iqbal M, Ayesha H. Aminoacidopathies: Prevalence, Etiology, Screening, and Treatment Options. Biochem Genet 2018;56:7-21.
6. Horvath GA, Blau N, Ferreira CR. Clinical and biochemical footprints of inherited metabolic disease. V. Cerebral palsy phenotypes. Mol Genet Metab 2021;S1096-7192(21)00071-8.
7. Ghaziuddin M, Al-Owain M. Autism spectrum disorders and inborn errors of metabolism: an update. Pediatr Neurol 2013;49:232-6.
8. Elmonem MA, Belanger-Quintana A, Bordugo A, Boruah R, Cortès-Saladelafont E, Endrakanti M, 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;131:285-8.
9. Grantham-McGregor S, Cheung YB, Cueto S, Glewwe P, Richter L, Strupp B, et al. Developmental potential in the first 5 years for children in developing countries. Lancet 2007;369:60-70.
10. Akin EÖ, Pekcici BB, Eminoglu FT. International classification of functioning, disability and health framework (ICF) based adaptive functioning outcomes of children with organic acidemias from a middle-income country. Brain Dev 2021;43:389-95.
11. 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;16:119.
12. Bronfenbrenner U. Ecological models of human development. 2nd ed. New York: Freeman 1993.
13. Özalp Akin 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;7:107.
14. Bingoler Pekcici EB, Özalp Akin E, Ayranci Sucakli I, Kara Elitok G, Onat FN, Kivilcime M, et al. Addressing early childhood development and developmental difficulties in Turkey: a training programme for developmental pediatrics units. Arch Argent Pediatr 2020;118:e384-91.
15. Parker S, Greer S, Zuckerman B. Double jeopardy: the impact of poverty on early child development. Pediatr Clin North Am 1988;35:1227-40.
16. Liu S, Lombardi J, Fisher PA. The COVID-19 Pandemic Impact on Households of Young Children With Special Healthcare Needs. J Pediatr Psychol 2022;47:158-70.
17. Oge Enver E, Hopurcuoglu D, Ahmadzada S, Zubarioglu T, Aktuglu Zeybek AC, Kiykim E. Challenges of following patients with inherited metabolic diseases during the COVID-19 outbreak. A cross-sectional online survey study. J Pediatr Endocrinol Metab 2020;34:103-7.
18. Siddiq S, Wilson BJ, Graham ID, Lamoureux M, Khangura SD, Tingley K, et al. Experiences of caregivers of children with inherited metabolic diseases: a qualitative study. Orphanet J Rare Dis 2016;11:168.
19. Engle PL, Fernald LC, Alderman H, Behrman J, O'Gara C, Yousafzai A, et al. Strategies for reducing inequalities and improving developmental outcomes for young children in low-income and middle-income countries. Lancet 2011;378:1339-53.
20. Black MM, Walker SP, Fernald LCH, Andersen CT, DiGirolamo AM, Lu C, et al. Early childhood development coming of age: science through the life course. Lancet 2017;389:77-90.
21. Ertem IO, Krishnamurthy V, Mulaudzi MC, Sguassero Y, Bilik B, Srinivasan R, et al. Validation of the International Guide for Monitoring Child Development demonstrates good sensitivity and specificity in four diverse countries. Acta Paediatr 2019;108:1074-86.
22. Raut A, Mustafayev R, Srinivasan R, Chary A, Ertem I, Grazioso M, et al. Hybrid type 1 effectiveness/implementation trial of the international Guide for Monitoring Child Development: protocol for a cluster-randomised controlled trial. BMJ Paediatr Open 2021;5:e001254.
23. Ozalp Akin E, Akbas A, Atasoy SC, Kanatli MC, Ince Acici S, Mustafayev R, et al. Applicability of the Guide for Monitoring Child Development as a Telehealth Delivered Intervention During the Pandemic. Front Pediatr 2022;10:884779.