KAYSERI CHILD HEALTH ASSOCIATION

JP

The Journal of PEDIATRIC ACADEMY

Year 2023
Volume 4 | Issue 1

e-ISSN: 2718-0875

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The Journal of Pediatric Academy is the official publication of the Kayseri Child Health Association.

The Journal of Pediatric Academy which was established in 2020 is an international, unbiased double blinded peer-reviewed, open-access electronic and only-online published journal in the English language. The Journal of Pediatric Academy is published 4 times a year (March, June, September, December) and accepts original research articles, invited review articles, case reports and clinical images in all areas of pediatric research, which summarize recent developments about a particular subject based on standards of excellence and expertise.

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Journal Name	Journal Short Name	Publishing Language	Broadcast Period	ISSN/E-ISSN
The Journal of Pediatric Academy	J. Pediatr. Acad. (JPA)	English	4	-

Starting Date	Publication Type	Indexed	Journal Concessions
2020	Periodicals (Online)	-	Kayseri Child Health Association

Journal Management Location and Address

The Journal of Pediatric Academy Office,
Kayseri Chamber of Medicine,
Seyitgazi Mah. Nuh Naci Yazgan Cad. Geriatri Merkezi Binası K:1 N:4, Melikgazi, Kayseri - Türkiye
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Journal of Pediatric Academy (JPA) reports on major advances in the diagnosis and treatment of diseases in children. Each issue presents informative original research articles, review articles, case reports, image corners, and letters to the editor from leading clinicians and investigators worldwide.

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Manuscript Types

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Letters to the editor should pertain to articles published within the Journal of Pediatric Academy or highlight important new clinical or laboratory insights. The text should contain 1000 words or fewer.

Table 1.
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Manuscript Type	Word Limit	Abstract Word	Limit Reference	Limit Table Limit	Figure Limit
Editorial comment	1500	No abstract	15	2	5
Original Article	3500	300	50	6	6
Invited Review	5000	350	100	6	10
Case Report	1500	200	15	2	5
Image corner	500	No abstract	5	-	3
Letter to the Editor	100	No abstract	5	1	1

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Cite unpublished data—such as papers submitted but not yet accepted for publication and personal communications, including e-mail communications—in parentheses in the text. If there are more than three authors, name only the first three authors and then use et al. Refer to the List of Journals Indexed in Index Medicus for abbreviations of journal names, or access the list at http://www.nlm.nih.gov/tsd/serials/lji.html. Sample references are given below:

Journal Article:

1. Ang KK, Price RE, Stephens LC, et al. The tolerance of primate spinal cord to re-irradiation. *Int J Radiat Oncol Biol Phys*. 1993;25:459–464.

Journal Article published in non-English Languages:

2. Altuntaş N, Çelebi DT, Koçak M, Andıran N. Yenidoğan bebeklerde direkt coombs testi taraması ve pozitifliğinin morbidite üzerine, etkisi; tek merkezd eneyimi. *Pam Tıp Derg* 2015;8:39-44. (in Turkish)

Book Chapter:

3. Dimery IW. Chemotherapy in head and neck cancer. In: Myerhoff WI, Rice DH, eds. Otolaryngology: head and neck surgery, 2nd ed. Philadelphia: WB Saunders, 1992:1027–1045.

Entire Book:

4. Virchow R. Cellular Pathology. Philadelphia: JB Lippincott, 1863.

Software:

5. Epi Info [computer program]. Version 6. Atlanta, GA: Centers for Disease Control and Prevention; 1994.

Online Journals:

6. Friedman SA. Preeclampsia: a review of the role of prostaglandins. Obstet Gynecol [serial online]. January 1988;71:22–37. Available from: BRS Information Technologies, McLean, VA. Accessed December 15, 1990.

Database:

7. CANCERNET-PDQ [database online]. Bethesda, MD: National Cancer Institute; 1996. Updated March 29, 1996.

World Wide Web:

8. Gostin LO. Drug use and HIV/AIDS [JAMA HIV/AIDS Web site]. June 1, 1996. Available at: http://www.ama-assn.org/special/hiv/ethics. Accessed June 26, 1997.

URL (Uniform Resource Locator)

9. (J. M. Kramer, K. Kramer [jmkramer@umich.edu], e-mail, March 6, 1996).

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Web: www.galenos.com.tr **Publisher Certificate Number:** 14521

Publication Date: March 2023
E-ISSN: 2718-0875
International scientific journal published quarterly.

Contents

Journal of Pediatric Academy

Invited Review

Year: 2023 Volume: 4 Issue: 1
Doi: 10.4274/jpea.2023.218
J Pediatr Acad 2023; 4: 1-5

Inherited Bone Marrow Failure Syndromes in Children

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Article Information

Article Type: Invited Review
Article Group: Pediatric Hematology

Received: 14.03.2023
Accepted: 24.03.2023
Available Online: 31.03.2023

Cite this article as: *Ertunç ME, Çelik AG, Tahiroğlu A, Ünal E. Inherited Bone Marrow Failure Syndromes in Children. J Pediatr Acad 2023; 4: 1-5*

Abstract

Inherited bone marrow failure syndromes are disorders of hematopoiesis that are mostly encountered in childhood. Taking the basis from genetics, they are characterized by pancytopenia, increased risk of developing myelodysplastic syndrome and malignancy. Extrahematopoietic presentations are observed often in addition to symptoms related to defective hematopoiesis (also known as bone marrow failure). The biology, clinical features, and management of the main syndromes such as Fanconi anemia, dyskeratosis congenita, Shwachman-Diamond syndrome, congenital amegakaryocytic thrombocytopenia, Diamond-Blackfan anemia, and severe congenital neutropenia are briefly summarized in this review.

Keywords: Inherited bone marrow failure syndrome, children, pancytopenia, fanconi anemia, dyskeratosis congenita

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Introduction

Inherited bone marrow failure syndromes (IBMFS) are rare syndromes of defective hematopoiesis that are associated with extra-hematopoietic manifestations. There can be a broad range of clinical presentations of IBMFS from immune deficiency to structural abnormalities.[1] Besides this spectrum of symptoms, there is also an increased risk of malignancies. IBMFS show diminished or total absence of hematopoietic precursors in the bone marrow, therefore generation of hematopoietic lineages gets affected. Early diagnosis of these conditions is crucial to prevent systemic complications while taking precautions for life-threatening complications that require urgent intervention. Furthermore, with the help of early diagnosis and earlier intervention, we may delay the disease progression and that would give us the necessary time to plan further optimal management options.

With the recent developments in molecular genetics, the disease-causing mechanisms have been better elucidated. Currently, more than 100 genes linked with these syndromes have been identified. Understanding the genetic background has made it easier to classify these diseases and then tailor the treatment accordingly. It was found that Fanconi anemia (FA) is related to deoxyribo nucleic acid (DNA) repair genes, dyskeratosis congenita (DC) is related to telomere maintenance genes, Shwachman-Diamond syndrome (SDS) and Diamond-Blackfan Anemia (DBA) are related to ribosome biogenesis or function genes. A better comprehension of these diseases improves the optimal management of the related complications.

Currently, hematopoietic cell transplantation (HCT) is the only viable curative treatment for the hematological manifestations of most IBMFS; with that being said, it doesn't treat the non-hematological findings and it should be kept in mind that, during the HCT there is a significant increase in malignancy development risk in addition to HCT related complications.[2] In the future, we may hopefully see gene therapies' successful implementation from the lab to the clinic. Finally, a holistic approach to patients is the clinician's duty which includes genetic counseling, psychological support and palliative care.

Fanconi Anemia

FA is a chromosomal instability disease that is mostly related to autosomal recessive mutations but on top of that some types have autosomal dominant and X-linked recessive forms.[3-5] To the best of our knowledge, there are at least 22 DNA repair genes in the FA/BRCA pathway that are implicated in the pathogenesis of FA. They take part in aldehyde detoxification, oxidative phosphorylation, proinflammatory and myelosuppressive cytokine homeostasis, and cell cycle regulation via p53/p21. Deterioration of these functions in hematopoietic stem cells causes bone marrow failure (BMF).[4,6]

Generally, patients with FA have variable levels of pancytopenia in childhood. Besides thumb and radial ray malformations, microcephaly or hydrocephaly, renal malformations, short stature, and café-au-lait spots are the most frequent clinical features, however 35% of the patients do not have any of those.[3-5] FA can present with acute myeloid leukemia (AML), cancers of the head & neck, vulva, esophagus and brain; developmental malformations, extreme sensitivity against the proinflammatory cytokines and alkalizing agents besides BMF.[4,6] Among various IBMFS, FA has the highest cancer incidence which is a consequence of defective DNA repair.[5] Since the cells of FA patients are sensitive to crosslinking agents like diepoxybutane (DEB) and mitomycin C (MMC) this quality is used as a screening test that involves controlled exposure of these agents to the cells derived from the peripheral blood for most of the time. A positive result which is defined as having a significant increase in chromosomal breakage; will require genetic testing to confirm and identify the defect precisely. If DEB and MMC test results came back negative although there is a high pre-test probability, a second test using skin fibroblast should be considered which can be of use because there can be false negatives due to the possibility of normal DNA repair in T-cells due to somatic mosaicism or revertant mutations as well as patients which already undergone HCT.[4,7] But at the summit of diagnostic tools stays the molecular genetic tools. With the wide availability of next generation sequencing in which sequencing is done at multiple DNA fragments in a parallel way, much faster and cheaper compared to conventional Sanger sequencing. Now single DNA sequencing with a promise of eliminating errors of amplification and offering a more detailed picture of the genome is on the way. These molecular tools started to change clinical practice in many areas and will keep being.[8]

Following the diagnosis of FA, patients should undergo baseline extensive multiorgan assessment and enter a monitoring plan designed with follow-up by an experienced hematology-oncology center. Currently, the only cure for BMF is HCT although ongoing research and development in gene therapy utilizing gene-corrected $CD34^+$ stem cells from FA patients have been found to be engrafted in immune-deficient mice can be a promising option but clinical application efficacy is not yet demonstrated.[9,10] The goal of the BMF monitoring plan is to intercept at the best time for the HCT and to evaluate the severity of cytopenia, dysplastic or neoplastic features in the bone marrow, the presence and type of cytogenetic abnormalities, infections, transfusion loads, types of available donors, availability of stem cells, and effectiveness of treatment without HCT. HCT increases the risk for secondary malignancies therefore patients who are considered to undergo or already underwent HCT should be evaluated carefully.[2,6]

Dyskeratosis Congenita

DC is a rare multisystemic inherited disorder of telomers that is characterized by BMF, and ectodermal features. Shortening of telomers causes genetic damage whereas normally long repetitive sequences of TTAGGG at the end of chromosomes prevent the loss of genetic material during each cell division.[11] DC has been associated with 12 different genes. The most common mutation is in the *DKC1* gene with X-linked recessive inheritance (20%-

25%). Other related genes are *TERT, ACD* and *RTEL1* which are inherited as (Autosomal Dominant, Autosomal Recessive) // *TERC, TINF2* (Autosomal Dominant) // *NHP2, NOP10, PARN, WRAP53, DCLRE1B* (Autosomal Recessive) // *TYMS* (Digenic Dominant).

DC is characterized by a dysplasia triad consisting of unusual skin pigmentation (Reticulated skin pigmentation, generally on the upper body and the neck), nail dystrophy and leukoplakia of oral mucous membranes. This triad is useful for diagnosis but not always all 3 findings present at the same time. Skin pigmentation and dystrophic nail changes are usually the first recognized features.[5,11]

The leading causes of mortality in DC are complications related to pancytopenia with 60-70%, pulmonary disease with 10-15%, and malignancies with 10%.[11] BMF can develop at any age and it may even be the first clinical manifestation of DC. Epiphora (tear duct obstruction), learning difficulties, developmental delay, mental retardation, pulmonary disease, short stature, esophageal strictures, hair loss at an early age (whitening), tooth decay, and tooth loss can be seen.[11] Cerebellar hypoplasia can be encountered in radiological studies. Patients with DC are at high risk of developing various cancers. While this rate is less than 10% before the age of 20, it increases to 20-30% at the age of 50. The average age of cancer diagnosis is 29 (up to 1.5-68 years old).[12]

Hoyeraal-Hreidarsson Syndrome (HHS) is a clinically severe form of DC. Symptoms of the disease begin in early childhood. HHS is a multisystem disease characterized by BMF, immunodeficiency, and severe growth retardation. HHS is associated with the *DKC1* gene. Also, the *DKC1* gene which encodes the dyskerin protein is the cause of X-linked DC. Most of those with the pathogenic variants of *DKC1* have the classic DC phenotype. Subgroups of some *DKC1* variants have the HHS phenotype.[11,13]

Molecular sequencing confirmed with functional tests such as telomere length analysis, short telomeres, and clinical findings can be counted among the best diagnostic modalities.

As the treatment, blood transfusions, antimicrobials, and antifibrinolytic agents can be considered. Currently, HCT is the only viable curative option for BMF in DC patients.

Androgens, Granulocyte colony-stimulating factor (G-CSF), and erythropoietin treatment can be used in patients who cannot be treated with HCT, but the responses are temporary.

Diamond-Blackfan Anemia

Genes related to DBA are essential for ribosome assembly and function.[5] In DBA, the most common disease driver variants are autosomal dominant missense mutations involving the *RPS19* gene.[14,15] Besides that *GATA1*-related and *TSR2*-related DBA are inherited in an X-linked manner.[15] As a result of these mutations, small or big subunits of ribosomes are affected and the number of functional ribosomes in cells is decreased.

DBA is generally characterized by erythroid hypoplasia and 95% of diagnosis is made in the first two years of life. Typically patients have macrocytic anemia and reticulocytopenia however granulocyte, lymphocyte, and megakaryocyte counts are normal.[5,14,15] Along with it, erythroid colony-forming units are extremely reduced and erythrocyte adenosine deaminase levels are usually elevated.[14] Craniofacial anomalies (cleft palate and lip), thumb deformations, and growth failure are the most frequent physical anomalies seen in DBA patients. Besides, the risk of developing cancer and myelodysplastic syndrome is increased in these patients.[14,15] Steroids, chronic red blood cell transfusion, and HCT are some options that could be considered in the treatment of DBA.

Shwachman-Diamond Syndrome

SDS, the third most common IBMFS after FA and DBA; is an autosomal recessive disorder that is characterized by the triad of BMF, exocrine pancreas deficiency, and skeletal anomalies.[16,17] The most common gene in association with SDS is the *SBDS* gene which is found in the majority of patients.[17] Although the role of the *SBDS* gene is not fully understood, it plays a role in ribosomal maturation, cell proliferation, and the hematopoietic microenvironment. Studies showed that the *SBDS* gene is also involved in telomere length maintenance and even heterozygous variants in *SBDS* has shown to be related to acquired aplastic anemia.[18] Other than the *SBDS* gene; *DNAJC21, EFL1,* and *SRP54* genes are also involved in ribosome assembly and protein translation. Patients with mutations of these genes present with the SDS phenotype.[17] In addition to skeletal anomalies in patients with *DNAJC21*; gingivitis, dental caries, and microdontia are also observed on oral examination.[19]

MDS and AML have been seen in up to one-third of SDS patients. (OMIM260400)[20] Exocrine pancreatic insufficiency is usually the first complaint in patients with SDS although systemic manifestations include nervous, cardiac, endocrine, immune and skeletal systems.[21]

The mean age at diagnosis for SDS is 1.3 years (0-35.6 years).[22] Neutropenia and steatorrhea are seen in 51% of those with mutations in the *SBDS* gene. In the other 14%, there was no evidence of cytopenia at the initial admission. Pancreatic lipomatosis is also seen in imaging. Normal fecal elastase levels and normal skeletal imaging do not exclude the diagnosis of SDS.[17] Typically, neutropenia is observed but other cytopenias can also be present. Neutrophil chemotaxis and migration defects can also be observed in addition to neutropenia.[23] With exocrine pancreatic insufficiency, problems occur in the digestion of fats and fat-soluble vitamins. Therefore, steatorrhea, foul-smelling defecation, and growth retardation are seen. Pancreatic findings appear at 6-12 months of age. Over time, the medical condition of patients improves and they stop taking pancreatic enzyme (NE) therapy.[24] Diabetes mellitus and endocrine pancreatic disorders are unrelated to SDS. Hepatomegaly and elevated transaminases can also occur. Short stature, osteopenia, metaphyseal dysplasia, thoracic and pelvic dysplasia,

short extremities can be seen. Worm-like skull bones can be observed due to abnormal bone turnover and decreased osteoclast and osteoblast activity. Mineral deficiency due to pancreatic insufficiency causes an increase in bone findings. Vertebral compression fractures may occur.[17] Some patients may have learning and behavioral disorders like attention deficit hyperactivity disorder.[25]

Once the diagnosis is confirmed, patients should be initiated pancreatic NE replacement. Fat-soluble vitamin levels should be checked every 6-12 months and replaced if needed. If anemia or thrombocytopenia develops appropriate transfusions are recommended. As a result of transfusions, iron chelation should be considered if necessary. In the presence of severe neutropenia, prophylactic antibiotics can be used. G-CSF can also be used to raise white blood cells. HCT is the only curative treatment option that may be done in selected cases.

Congenital Amegakaryocytic Thrombocytopenia (CAMT)

CAMT is associated with a very low number of megakaryocytes in the bone marrow starting from the neonatal period. At first, a problem solely in the thrombocytic series arises, but in the progress of time, the condition worsens and all lineages are affected resulting in pancytopenia. CAMT is an autosomal recessive disease and has been classified into two types; type 1, the severer form, in which variants in *MPL* gene as frameshift or stop codon mutations causes a complete loss of receptor function leading to decreased bone marrow activity and early-onset low platelet count around 2 years of age.[26] Whereas in type 2 the milder one, platelet numbers are generally normal in infancy, later leading to BMF around 4 years of age which is due to variants that cause splicing defect or amino acid substitution that can lead to the problem in *MPL* receptor's glycosylation resulting to decreased response to thrombopoietin or causes hydrogen bonds to be lost within the *MPL* receptor making it unstable although residual receptor function is preserved.[26-29]

CAMT usually arises in consanguineous marriages, more commonly in women. A misdiagnosis as neonatal alloimmune thrombocytopenia (NAIT) is a possibility. For this reason, the incidence appears to be less. The incidence of NAIT is 1 in every 1,000 live births. On the other hand, approximately 100 CAMT cases have been reported so far.[29,30] CAMT is not accompanied by skeletal anomalies which is an important thing to consider in the differential diagnosis of IBMFS.[31]

CAMT usually presents with thrombocytopenia in the first month of life or fetal life leading to petechiae, intracranial hemorrhages, recurrent rectal hemorrhages, and pulmonary hemorrhages.[28] Also growth and developmental retardation, strabismus, central nervous system anomalies, cerebral malformations, and cortical dysplasia can accompany. If any congenital anomaly is found on physical examination, the diagnosis of CAMT should be re-evaluated.[29]

The mean platelet count in patients with CAMT is 20,000/mm^3. Bone marrow biopsy should be evaluated in every child with congenital thrombocytopenia. *MPL* gene test should be performed according to the results of megakaryocyte evaluation in the biopsy. Platelet transfusions can be needed as a supportive treatment. If anemia or neutropenia has also developed, antimicrobials or red blood cell transfusions can be performed in proper conditions. Antifibrinolytic agents can be used for bleeding control. HCT is the only curative treatment option. HCT should be done as early as possible. It should be done before pancytopenia develops however there is no exact optimal time.

Severe Congenital Neutropenia (SCN)

In SCN in which there is a mature neutrophil deficiency in the bone marrow, the average absolute neutrophil count is less than 200/μL and it often coexists with the elevated number of monocytes.[32] The mode of inheritance can be single gene mutation, X linked or sporadic. The most frequent mutation seen in patients in the population of non-consanguineous marriage emerges on the *ELANE* gene which encodes the neutrophil elastase NE whereas in a population with high consanguineous marriage *HAX1* gene is determined to be the most common one.[5,33,34] NE is a serine protease that can hydrolyze some bacterial and extracellular matrix components and it is essential in innate immunity. Pathogenicity of ELANE mutations is mostly explained by mutant NE which causes developing neutrophils to go apoptosis which leads to low neutrophil counts.[33] Also *GFI1, CSF3R*, *G6PC3, VPS45, WAX, SRP19, SRPRA* genes are reported. Studies keep revealing novel genetic variants related to SCN.[35-37]

Patients with SCN have an increased risk of developing MDS and AML. Persistent severe neutropenia, (<500/μL) recurrent bacterial infections, and maturation arrest in bone marrow can be established in patients with SCN as clinical symptoms and no other congenital malformations are present.[5,33] Preventing infections is extremely important in the treatment of SCN. Therefore, the first-line drug in SCN is G-CSF, with a response rate of approximately 90%.[33]

Conclusion

IBMFS are rare and critical illnesses. It is crucial to perform a physical examination and take a family history in patients who are not expected to have cytopenia especially in the pediatric population. For management, the level of the disease should be determined by performing genetic studies and laboratory tests. Clinicians should be vigilant about the increased risk of malignancy. Prompt evaluation and initiation of the treatment are essential.

Author Contributions: All authors certify that she has participated sufficiently in the intellectual content, the analysis of data. Each author has reviewed the final version of the manuscript and approves it for publication.

Conflict of Interest: All authors also disclose no conflict of interest that may have influenced either the conduct or the presentation of the research.

Financial Disclosure: The authors have no conflicts of interest to declare.

Informed Consent: The corresponding authors declare that there is not any acknowledgments or disclaimers.

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Journal of Pediatric Academy

Original Article

Year: 2023 Volume: 4 Issue: 1
Doi: 10.4274/jpea.2023.213
J Pediatr Acad 2023; 4: 6-11

Vitamin D, Insulin Resistance and Cytokine Levels in Obese Pubertal Children

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Article Information

Article Type: Original Articles
Article Group: Pediatric Endocrinology

Received: 13.01.2023
Accepted: 07.03.2023
Available Online: 31.03.2023

Cite this article as: *Kirkiz Kayalı S, Cinaz P, Bideci A. Vitamin D, Insulin Resistance and Cytokine Levels in Obese Pubertal Children. J Pediatr Acad 2023; 4: 6-11*

Abstract

Insulin resistance (IR) develops in obese children because of low vitamin levels and increased pro-inflammatory cytokine levels. This study aimed to analyze the relation between vitamin D, insulin resistance, tumor necrosis factor-alpha and interleukin 6 (IL-6) levels at admission and after weight loss. This study included 84 obese and 28 healthy pubertal children. Patient group was divided into four: IR positive and negative; weight loss (WL) positive and negative. Baseline and follow-up (6th month) values of serum 25-hydroxyvitamin D and other parameters were evaluated. The prevalence of serum vitamin D deficiency and insufficiency were 3.6% and 21.4% in the control group, 15.2% and 10.9% and 7.9% and 15.8% in the obese insulin positive and negative group; respectively. There was no relationship between vitamin D and IRand IL-6 levels, whereas cytokine levels were lower in obese children. As WL increased, vitamin D level and IR improved. No significant difference was found between vitamin D levels of obese and control subjects. In obese children with weight loss, an insignificant increase was observed in vitamin D, cytokines, quantitative insulin sensitivity check index values and an insignificant decrease was noted in homeostatic model assessment for IR value. Further longitudinal studies with larger patient series with greater WL are warranted.

Keywords: Insulin resistance, interleukin 6, obesity, tumor necrosis factor alpha, vitamin D

Introduction

Obesity is an important health problem, the frequency of which increase in all age groups. There are more than 43 million overweight or obese children in the world.[1] According to the Turkish Statistical Institute, obese individuals over 15 years constituted 19.6% of the population in Turkey in 2016.[2] Numerous etiologic factors such as genetic predisposition, nutritional habits, hormones, sociocultural factors, sedentary life, and drug use could cause obesity. Furthermore, childhood obesity leads to diabetes, hypertension, cardiac diseases, and respiratory system problems in adulthood.[1,3]

Vitamin D deficiency is a prevalent health issue causing rickets and osteopenia in children. It has an essential role in calcium (Ca) metabolism, cell differentiation and replication, glucose homeostasis, insulin secretion, immunological response, and inflammation-related obesity.[4] Recent studies have revealed a correlation between childhood obesity and low vitamin D levels.[5,6] Deficiency of vitamin D results when parathyroid hormone (PTH) concentration, the transformation of serum 1,25 hydroxy vitamin D

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[1,25(OH)2D] and Ca migration to adipose tissue increase. These lead to increased inhibition of lipolysis mediated through the stimulation of phosphodiesterase 3B and increased lipogenesis through the stimulation of fatty acid synthase. Additionally, increased PTH directly suppresses lipid oxidation in the muscle tissue.[7]

Insulin resistance (IR) has also been related to vitamin D deficiency.[8,9] Moreover, excess body weight (BW) increases adipose tissue, impairs its distribution and functions, promotes macrophage migration and transformation, increases the release of proinflammatory cytokines, and impairs insulin sensitivity.[5]

Highlights

- Obesity is a growing worldwide health problem with an increasing prevalence in children.
- Obese children have a higher risk of low 25(OH)D.
- Hypovitaminosis D is associated with abnormal glucose homeostasis and inflammatory cytokines.

The prospective study aimed to explore levels of vitamin D, proinflammatory cytokines, and IR measured at the initial diagnosis and a six-month follow-up in obese children with or without weight loss (WL).

Material and Method

This prospective study included 84 pubertal obese children who were admitted to the pediatric endocrinology outpatient clinic between January 2009 and June 2009. The patients presented either with a complaint of obesity or they had been referred from another outpatient clinic because of a body mass index (BMI) ≥95th percentile. Pubertal development was defined as the development of the breast in females and the testicular volume of 4 mL in males (Tanner stage 2).

The control group consisted of 28 pubertal healthy children, whose ages were similar. Patients with endocrine obesity and chronic liver or kidney disease, those using vitamin D supplementation, anticonvulsant drugs or steroids were excluded from the study. The local ethics committee approved the research (number 410, date:22.12.2008). Informed consent was obtained from the parents of the patients. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

In order to evaluate the nutritional status of patients, a three-day retrospective food consumption record was requested. According to the values of the World Health Organization, the daily energy required by the patients was calculated. The activity level of the patients was followed up with physical activity diaries. The daily intake of Ca was calculated using the Nutrition Information System computer application according to the food consumption record of the patients. The patients confirmed that they adhered to their diet protocol included in the study.

BW was assessed using an electronic scale while subjects were in a standing position in light clothes and bare feet. Body height was measured in a standing stance using a wall-mounted stadiometer (Harpenden, UK). BMI was calculated and evaluated as defined [Normal BMI: 85 kg/m^2, overweight BMI: 85-95 kg/m^2, obesity BMI over 95 kg/m^2.[10] The LMS approach was used to analyze BMI standard deviation (SD) scores (BMI-SDS).[11]

Fasting blood glucose (FBS), insulin, Ca, phosphorus (P), and alkaline phosphatase (ALP) levels were obtained from venous blood samples after a 12-hour fasting between January and June. PTH, tumor necrosis factor-alpha (TNF-α) and interleukin 6 (IL-6) samples were stored at -80 °C and measured using an immunoradiometric assay (BioSource, Nivelles, Belgium). The PTH, TNF-α, and IL-6 cutoff values were determined using the manufacturer's book, which were 6.87-64.87 pg/mL, 5 pg/mL, and 6-31 pg/mL, respectively. Radioimmunoassay (RIA) (BioSource, Nivelles, Belgium) was used to measure serum 25 Hydroxy vitamin D [25(OH)D] levels and it was evaluated as defined [adequate serum 25(OH)D: over 30 ng/mL, inadequate 20-29 ng/mL, deficiency less than 20 ng/mL].[12] Serum 1,25(OH)2D (range 19.6-54.5 pg/mL was also measured RIA.

The IR parameters including homeostatic model assessment for insulin resistance (HOMA-IR), fasting glucose/fasting insulin ratio (FGIR), and quantitative insulin sensitivity check index (QUICKI) were analyzed for each individual. Formulas applied for these calculations were described/reported in a different report.[13]

The patients were classified into four subgroups based on their IR status and the presence of WL at follow-up:

Group 1a: Obese pubertal children diagnosed with IR at the time of diagnosis,

Group 1b: Obese pubertal children diagnosed non-IR at the time of diagnosis,

Group 2a: Obese pubertal children without WL during follow-up,

Group 2b: Obese pubertal children with WL during follow-up,

Control group: Healthy pubertal children.

Statistical Analysis

All data was analyzed using Statistical Package for the Social Sciences version 22. The conformity of variables to normal distribution was assessed using the Shapiro-Wilk test. Categorical variables were expressed as frequencies (n) and percentages (%) and continuous variables were expressed as mean, SD, and minimum-maximum. The means of two independent groups were compared using Student's t-test and the means of more than three or more groups were compared using one-way ANOVA. Differences in the median values between groups were analyzed using Mann-Whitney U test for the comparison of two groups and Kruskal-Wallis H test for the comparison of more than two groups. Both One-Way ANOVA and Kruskal-Wallis H tests were followed by a post-hoc Tukey's test or non-parametric multiple comparison test, respectively, to identify the underlying reasons. In patients that had regular follow-up visits, baseline and follow-up laboratory parameters

were compared using Wilcoxon signed-rank test with Bonferroni correction. Categorical variables were compared using chi-square or Fisher's exact test. Correlations between continuous variables were assessed using Spearman's correlation coefficient. A p value of <0.05 was considered significant.

Results

Table 1 presents a comparison of the patient and control groups. The mean age of patients was 12.7 years (8.5-17.9).

While the patient group had more sun exposure and physical activity than the control group, no statistical difference was revealed. Although Ca consumption was below the recommended dose (1,300 mg/day for the 9-18 age group), Ca, P, ALP, 25OHD, 1,25(OH)2D and PTH measurements were within normal ranges for all groups, with no difference identified between the patient and control groups (**Table 1**).

Groups 1a and 1b

The mean age of group 1b was significantly lower compared to both group 1a (+) and the control group (p 0.05) (**Table 1**).

There was a significant difference in BW, BMI and Body mass index standard deviation score (BMI SDS) between the control group and groups 1a, 1b (p<0.001) (**Table 1**).

TNF-α levels were different compared to the control group and groups 1a, 1b (p<0.001). However, a comparison of groups 1a and 1b showed no difference. In the control group and group 1b, only IL-6 was different (p<0.05) (**Table 1**).

A significant difference was found in insulin, IR parameters between the control group and groups 1a and 1b (p<0.001 for all). However, no difference in these values was reported between the control group and groups 1b (p>0.05 for all) (**Table 1**).

Groups 2a and 2b

There was a significant difference in BW, BMI and BMI SDS between the control group and groups 2a, 2b (p<0.001) (**Table 1**).

The only significant difference between the control group and group 2a were in HOMA-IR and QUICKI values (p<0.05 for all) (**Table 1**).

Insulin, HOMA-IR measurements were observed to be higher in groups 2b and group 2a IR (-) than in group 2a IR (+) group. However, the FGIR level was lower in groups 2b and 2a IR (-) (**Table 1**).

Discussion

Obesity is an important problem worldwide in all age groups. Hypovitaminosis D is associated with abnormal glucose homeostasis and inflammatory cytokines.[14] In our study, pubertal obese and control

Table 1.
Demographic characteristics and laboratory parameters of groups 1, 2 and the control group

	Control group (n=28)	Group 1a (n=38)	Group 1b (n=46)	Group 2a (n=17)	Group 2b (n=12)
Age (years) (mean ± SD) **Gender (Female/Male)**	13.6±2.5 (10/18)	13.3±2† (20/18)	11.7±1.9** (24/22)	12.2±1.6 (8/9)	13.8±2.4 (6/6)
Body weight (kg) (mean ± SD)	47.2±8.7	78.8±17.7**††	66.2±12**	71±12.6**	78±18.5**
Height (cm) (mean ± SD)	156.8±11	158.8±10	152.5±9.2	157±7.9	163±10.2
BMI (kg/m²) (mean ± SD)	19.1±2.2	30.7±4.2**†	28.2±2.6**	28.7±3.3**	29±5.4**
BMI-SDS (mean ± SD)	1.1±8.6	2.5±0.6**	2.3±0.4**	2.2±0.6**	2.1±1**
Ca (mg/dL) (mean ± SD)	9.6 ±0.3	9.6±0.3	9.6±0.3	9.6±0.3	9.7±0.2
P (mg/dL) (mean ± SD)	4.3±0.6	4.2±0.6	4.4±0.5	4.4±0.5	4.1±0.6
ALP (U/L) (mean ± SD)	183.8±89.9	207.3±99	240.2±91*	210.8±90.1	180.7±83
Ca intake (mg/day)	303.5 (113-988)	381 (66-828)	315.5 (90-1461)		
25 (OH) D (ng/L) (mean ± SD)	39.1±14.6	43±20.6	41.3±21.1	54.9±40.6	44.2±14.1
1,25(OH)$_2$ D (pg/mL) (mean ± SD)	30.3±15.3	31±14.3	27±13	40.1±32.1	49±27.7
PTH (pg/L) (mean ± SD)	14.7±10	15.7±15.6	18±16.3	15.3±10.5	17±11.7
FBS (mg/dL) (mean ± SD)	85.3±6.4	88.6±7.6	85±6.5	87.3±6.6	88.2±6.4
Insulin (µU/mL) (mean ± SD)	9.8±6.9	21±6.7**††	10.9±2.4	15.3±9	14.4±8.1
FGIR (mean ± SD)	12.2±7.6	4.7±2.2**††	8.2±2.1	9.5±12	7.4±2.7
HOMA-IR (mean ± SD)	2.1±1.6	5±1.7**††	2.3±0.5	3.3±2*	3.1±1.8
QUICKI (mean ± SD)	0.35	0.3**††	0.3	0.3*	0.32
TNF-α (pg/mL) mean ± SD **[a](minimum, maximum)**	69.3±126 30 (0-603.9)	17±19** 17 (0-101.2)	14.1±11.8** 15.1 (0-35.1)	25.8±32.1 15.9 (0-30.8)	42±42.2 16.2 (0-39.2)
IL-6 (pg/mL) mean ± SD **[a](minimum, maximum)**	33±43.1 22.1 (0- 222.1)	16.3±13.8 12.4 (0.7-72.1)	15.4±15* 9.5 (0-85.1)	22.4±15.7 12.9 (0.7-85.1)	99.5±251.3 9.5 (7.2-41.3)

Control Group vs. Group 1a/1b, Control Group vs. Group 2a/2b *p<0.05 **p<0.001
Group 1a vs. 1b, Group 2a vs. 2b †p<0.05 ††p<0.001
[a]non-normally distributed data
IR; Insulin resistance, WL; Weight loss, SD; Standard deviation, BMI; Body mass index, BMI-SDS; Body mass index standard deviation scores, FBS; Fasting blood glucose, FGIR; Fasting glucose/fasting insulin ratio, HOMA-IR; Homeostasis model assessment-estimated insulin resistance, QUICKI; Quantitative insulin sensitivity check index, Ca; Calcium, P; Phosphorus, ALP; Alkaline phosphatase, PTH; Parathyroid hormone, TNF-α;Tumor necrosis factor-alpha, IL-6; Interleukin 6

groups were compared for age, BMI, 25(OH) D,1,25(OH)2D, PTH, IR, and inflammatory status. Age differences between the control and obese groups 1a and 1b were significant; however, we did not take this into account as they had all entered puberty.

Vitamin D insufficiency is mostly caused by inadequate sun exposure, limited dietary vitamin D intake, and gastrointestinal malabsorption. Some studies suggest that vitamin D is deficient in obesity due to its accumulation in adipose tissue and low bioactivity. On the other hand, some other studies have reported conflicting results on this issue. While some studies showed a reciprocal relation between obesity and vitamin D deficiency.[15,16] Oommen and Al-Zahrani[17] did not find any relation between vitamin deficiency and obesity. Thereby Çizmecioğlu et al.[18] found that vitamin D deficiency and insufficiency did not differ between normal, obese or overweight groups. In our study, deficiency of vitamin D along with insufficiency were found to be 3.6% and 21.4% in the control groups and 11.9% and 13.1% in the patient groups. However, unlike the study by Torun et al.[9], no difference was found between these groups ($p>0.05$), which implies that normal-weight children in Turkey should also be carefully followed for vitamin D insufficiency. Additionally, although both groups had lower Ca intakes for their ages, the patient group had higher levels of physical activity and winter sun exposure than the control group, which could explain the lower ratio of vitamin D deficiency in the patient group than expected.

Insufficient vitamin D consumption and inadequate Ca levels are associated with hyperparathyroidism and weight gain. PTH promotes the hydroxylation of serum 25(OH)D in the kidney, converting it to serum 1,25(OH)2D. In obesity, increased serum PTH enhances lipogenesis, thus promoting Ca^{+2} influx into adipocytes, ultimately impeding catecholamine-induced lipolysis implications.[19] Bolland et al.[20] showed that patients with primary and secondary hyperparathyroidism have excess BW and fat mass. Tzotzas et al.[21] reported that the 25(OH) D level was lower in obese patients than the control groups. However, PTH levels were not different. They investigated the effects of a low-calorie diet on PTH and 25(OH)D levels in obese patients and although there was a negative correlation between 25(OH)D and PTH no significant change was seen in PTH levels after the diet. Furthermore, Reinehr et al[7] followed 133 obese children for an intervention program lasting one year. Initially, PTH levels were higher in obese children, whereas 25 (OH) D levels were higher in the control group. A slight WL resulted in considerable alterations in 25 (OH) D and PTH. In our research, the serum 25 (OH)D, 1,25 (OH)2D, and PTH levels between the patient and control groups before and after WL were not different ($p>0.05$). No significant variance in PTH concentrations between the two groups and the normal Ca^{+2} and P levels of patient groups suggests that the Ca homeostasis of the patient groups was unaffected. This could be a result of the fact that our study had only a limited number of participants and a short (6-month) period of observation.

Vitamin D affects insulin secretion and sensitivity of the adipose tissue in obesity. It is also known to cause vitamin D receptor (VDR) activation in pancreatic beta cells, 1α-hydroxylase expression, and local synthesis of serum 1,25 (OH) 2D either directly or through its paracrine effects. Additionally, it has a role in intracellular Ca^{+2} concentration and Ca^{+2} transport across cellular membranes. Insulin secretion and tissue insulin sensitivity are Ca-dependent mechanisms and vitamin D positively affects insulin receptor expression in peripheral cells.[5] Therefore, it is expected that vitamin D administration would enhance insulin sensitivity and function. Numerous studies have demonstrated that inadequate vitamin D results in impaired glucose homeostasis.[22,23] In contrast, Javed et al[24] reported no improvements in insulin action or beta-cell function after vitamin D treatment. Besides a placebo-controlled clinical study in obese adolescents showed IR or secretion parameters were not improved by vitamin D administration.[25] Although there was no significant difference in FBS levels between our control and obese groups, a significant difference was found in IR parameters (FGIR, HOMA-IR, and QUICKI). However, vitamin D deficiency or insufficiency did not differ between the obese IR (+) and IR (-) groups.

There are several studies on the changes in vitamin D levels and IR parameters after weight loss. and Tüfekçi[26] found that there was no significant improvement in IR parameters in obese women with vitamin D deficiency after weight loss. In our study at 6-months, although no significant difference was found between groups 2a and 2b in IR parameters, these parameters were closer to normal ranges in group 2b than group 2a. After WL with a short-term diet, IR parameters were improved, however statistical analysis could not be performed due to small number of patients of the six IR (+) patients with WL, five had adequate vitamin D levels, whereas one patient needed vitamin D supplementation. In one out of the five subjects who had normal vitamin D levels, vitamin D levels decreased to 20-30 ng/mL during the follow-up stage. Moreover, in three of these patients, IR parameters improved following WL.

Adipose tissue is contemplated as an endocrine organ that actively secretes cytokines known as adipokines. In obese individuals, cytokines secreted from dysfunctional adipose tissue (TNF-α, and IL-6) cause chronic low-grade inflammation. TNF-α and IL-6 have been associated with obesity and the development of type 2 diabetes. These cytokines also play an important role in energy balance, lipid and carbohydrate metabolism and control of inflammatory and immune responses.[19,27] Voltage dependent resistor receptors are expressed in immune cells such as antigen-presenting cells and active T lymphocytes. On the other hand, 1,25(OH) D treatment inhibits T lymphocytes, thereby altering their cytokine secretion profiles. Although some studies have reported a negative correlation between serum 25(OH) D and TNF-α, others have reported no significant relationship between serum 25(OH) D and IL-6.[24,28-30] In our study, TNF and IL-6 levels in the control group were higher than vitamin D deficient obese individuals ($p<0.001$

and p<0.05, respectively). Yet, while some studies found increased IL-6 levels in obese children, some others reported increased IL-6 levels in healthy children which were attributed to the discrepancy of the age, sex, daily intensive exercise, and diet in a recent study.[31-35]

Our findings might have been affected by several factors including limited number of patients, compliance of pediatric patients, and extra more time for WL. However whether vitamin D deficiency is a cause or consequence of obesity still remains controversial. Further longitudinal studies with large patient series are needed to substantiate our findings.

Conclusions

In conclusion, obesity is a complex disease, and the possible mechanisms associated with hypovitaminosis D, and IR are not fully described. In this present study, as expected, IR parameters were higher in the obese group (p<0.001). While there was no difference between the obese and control groups regarding vitamin D deficiency, we think that, in Turkey, not only obese children but also normal-weight healthy children could be at risk for vitamin D deficiency.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version. Kirkiz Kayalı S: Concept, Design, Data collection or processing, Analysis or interpretation, Literature search, Writing.; Cinaz P: Design, Analysis or interpretation, Writing; Bideci A: Design, Analysis or interpretation, Literature search, Writing.

Conflict of Interest: There are no conflicts of interest in connection with this paper, and the material described is not under publication or consideration for publication elsewhere.

Ethics Committee Approval: The study was carried out with the permission of Gazi University Ethics Committee (date: 22.12.2008, decision No: 2008/410).

Financial Disclosure: The authors have no conflicts of interest to declare.

Informed Consent: Informed consent was obtained from the parents of the patients.

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Journal of Pediatric Academy

Original Article

Year: 2023 Volume: 4 Issue: 1
Doi: 10.4274/jpea.2023.200
J Pediatr Acad 2023; 4: 12-17

The Predictors of Pneumonia in Children with COVID-19

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Article Information

Article Type: Original Articles
Article Group: Pediatric Rheumatology

Received: 03.11.2022
Accepted: 15.03.2023
Available Online: 31.03.2023

Cite this article as: *Yoldaş MA, Çelebi Tayfur A, Danış A, Hancı F, Atasoy Hİ, Bolu S, Coşgun Z, Kalfaoğlu ME, Kayış SA. The Predictors of Pneumonia in Children with COVID-19. J Pediatr Acad 2023; 4: 12-17*

Abstract

The purpose of this study was to evaluate the relationship between the presence of pneumonia and blood parameters in cases of Coronavirus disease (COVID-19) and to examine their predictive characteristics in terms of pneumonia. We reviewed the file records of 151 pediatric patients with a diagnosis of COVID-19 confirmed by the real time-reverse transcription polymerase chain reaction test in nasopharyngeal swabs. The patients were divided into two groups based on direct chest X-ray and computed tomography results in [Group 1 (n:41), with pneumonia findings, and Group 2 (n:110), with no pneumonia findings]. The groups' demographic data, clinical and laboratory findings were compared. Pulmonary involvement was determined in 41 (27.1%) of the 151 patients. The [body mass index (BMI) Z-score], red blood cell distribution width (RDW), mean platelet volume (MPV), neutrophil lymphocyte ratio, passive leg raise, and D-dimer levels were significantly higher in patients with pneumonia than those without pneumonia in our study. Based on multivariate logistic regression analysis, BMI Z-score, MPV, and RDW were found to be independent risk factors of pneumonia in patients. The current study showed higher levels of blood parameters in patients with coronavirus disease 2019 (COVID -19) presenting with pneumonia than those without pneumonia. We suggest that BMI-Z score and MPV value may assist in predicting pulmonary involvement in patients with COVID-19.

Keywords: Children with COVID-19, pneumonia, body mass index, hematological parameters

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Introduction

Coronavirus disease (COVID-19) has spread rapidly across the world since it was initially declared a pandemic by the World Health Organization on 11 March 2020[1]. The disease involves a wide spectrum, ranging from asymptomatic infection to severe pneumonia, acute respiratory distress syndrome, multiple organ failure, and death. In children, it is generally mild or moderate. However, pneumonia and systemic involvement have been reported in severe cases[2]. COVID-19 pneumonia is highly contagious, with a reported prevalence in children of 1.7-2.4%[3]. Due to its rapid progression and potentially fatal course, appropriate diagnostic and therapeutic approaches are of vital importance. The real-time reverse transcription-polymerase chain reaction (RT-PCR) is the primary method in the diagnosis of COVID-19. However, particularly in the early period from the disease or in the case of a low viral load, nasopharyngeal swab (RT-PCR) tests can be negative[4]. Pulmonary computed tomography (CT) and chest X-ray play an significant in the diagnosis of COVID-19, in the evaluation of the severity of pneumonia, in the detection of potential complications such as pulmonary embolism or pneumothorax, and patient follow-up[5]. A chest X-ray is the imaging method of choice for protection against radiation in children with suspected COVID-19 pneumonia. However, thoracic CT can be applied when necessary for diagnosis and treatment evaluation. Due to the low number of pediatric cases, and their milder clinical course, studies on the subject in the literature are insufficient[6]. The severe inflammatory reactions in COVID-19 can result in a cytokine storm and death. The immune response and cellular breakdown triggered by the rapid viral replication of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) lead to monocyte and macrophage accumulation and cytokine and chemokine release. Increased release and transcription of proinflammatory cytokines result in the elevated plasma levels cytokines and may lead to a cytokine storm[7].

Highlights

- COVID-19 pneumonia in children is seen with a frequency of 1.7-2.4%, and due to its rapid progression and fatal course, appropriate diagnosis and treatment approaches are vital.
- COVID-19 pneumonia can be severe in children, and we think that high BMI Z-score, MPV, NLR, PLR and D-dimer values are very important for rapid diagnosis and guiding treatment.
- We detected BMI-Z score, MPV and RDW values as independent risk factors in predicting pulmonary involvement in children with COVID-19.

Mutual interaction has been shown between these cytokines and several blood parameters in acute inflammation[8]. The predictive rate of peripheral blood parameters, the neutrophil/lymphocyte ratio (NLR), the platelet/lymphocyte ratio (PLR), red cell distribution width (RDW), and C-reactive protein (CRP) in determining the prognosis in systemic inflammatory diseases is still the subject of research. WBC count, NLR, PLR, and the lymphocyte-monocyte ratio are systemic inflammatory response markers employed as useful predictors of prognosis in viral pneumonia[9]. The aim of the study was to evaluate the association between blood parameters and pneumonia in cases of COVID-19 and to examine their predictive characteristics in terms of pneumonia.

Material and Method

Participants

In this retrospective study, 151 pediatric patients who were hospitalized in our Pediatrics Clinic between 01 May 2020 and 01 July 2021 and whose diagnosis of COVID-19 were confirmed by RT-PCR test on nasopharyngeal swabs were included in this retrospective study. Our study was carried out in accordance with the Declaration of Helsinki the patients and their families who participated in the study gave informed and written consent. The study protocol was approved by the local committee (Bolu Abant İzzet Baysal University Clinical Research Ethics Committee) for human studies (decision no: 2021/208, date no: 27.07.2021). Patients were seperated into two groups depending on their posterior-anterior direct chest X-ray and thoracic CT findings Group 1 (n:41) patients with pneumonia findings, and Group 2 (n:110), patients without pneumonia findings. Demographic data of patients from their file records and hemoglobin, hematocrit, mean erythrocyte volume, RDW, WBC count, neutrophil, lymphocyte and platelet counts, mean platelet volume (MPV), platelet distribution width, thrombocytcrit and glucose, aspartate aminotransferase, alanine aminotransferase, urea, creatinine, lactate dehydrogenase (LDH), fibrinogen and CRP levels at admission were evaluated. NLR and PLR values were calculated by dividing absolute neutrophil and platelet counts by lymphocyte counts, respectively, and body mass index (BMI) was calculated by dividing body weight (kg)/height^2 (m^2)[10]. The groups demographic data and clinical and laboratory findings were compared. Chest CT and chest X-ray findings were scanned and analyzed by two senior radiologists blinded to the identities and clinical data of the patients.

Statistical Analysis

Normality of variables was evaluated using the Shapiro-Wilk test. Descriptive statistics were obtained. Normally distributed continues variables were expressed as mean ± SD, while non-normally distributed numerical variables were expressed as median and interquartile range values. Categorical variables presented as number (percentages). Normally distributed continues variables were analyzed using the Student's t-test, and non-normally distributed numerical data using the Wilcoxon Rank Sum test. Categorical variables were analyzed using the chi-square (χ^2) test. Multiple explanatory variable logistic regression analysis was applied to determine the risk factors/covariates

for pneumonia. The initial model was fit including all significant independent variables. Then, a backward-elimination approach was conducted to evaluate the model for potential confounding effects. In this model, the factors/covariates were removed one at a time, starting with the factor/covariate that had the largest p value, until all remaining factors had a two-sided p value <0.05. The goodness of fit was tested using the Hosmer-Lemeshow test. Receiver-operating characteristic (ROC) curve analysis was used to determine the cutoff values of selected variables, via logistic regression, for pneumonia from the area under the curve (AUC). ROC curve analysis is carried out using "Optimal Cutpoints" library of R software. All statistical analyses were performed using the R software. A p value <0.05 were regarded as statistically significant for all analyses.

Results

COVID-19 pneumonia was present in 41 (27.2%) of the 151 patients. No pulmonary involvement was present in the other 110 (72.8%) patients. RT-PCR tests in terms of SARS-CoV-2 were positive in all patients. Ninety-three (61.6%) patients were boys, and 58 (38.4%) were girls. Pneumonia was detected in 25 (26.9%) boys and 16 (27.6%) girls. There was no significant difference between Group 1 and Group 2 in terms of the incidence of pneumonia. Unilateral right lung involvement and left lung involvement were observed in 16 (39.02%) and 6 (14.6%) on posterior-anterior chest X-rays of the 41 patients with pneumonia findings, respectively. Bilateral, predominantly peripheral multifocal involvement and consolidation areas were determined in 19 (46.34%) patients. The lower regions of the lungs were the most affected, with the right lower zone being affected in three patients (7.31%) and the left lower and left middle zones in two (4.87%). The right middle zone was affected in 13 patients (31.70%), the left middle zone in two (4.87%), and the left upper zone in two (4.87%) (**Figure 1**).

Bilateral diffuse peripheral predominant ground-glass opacities were determined in six (54.5%) of the 11 patients who underwent pulmonary CT, and unilateral diffuse peripheral predominant ground-glass opacities in five (45.5%). In those with unilateral pulmonary involvement, a diffuse ground-glass appearance was follow up in the right lung in 3 patients and the left lung in 1 patient, and a peripheral ground glass appearance was present in the left lung in one patient (**Figure 2**).

There was no statistically significant difference between the groups in terms of age, gender, length of hospital stay, ferritin, sedimentation, CRP or LDH values. Mean BMI value, BMI Z-score, NLR, PLR, and MPV values, and D-dimer levels were significantly higher among patients with pneumonia compared to those with no pneumonia (p<0.05), while mean lymphocyte and RDW values were significantly lower (p<0.05) (**Table 1, 2** and **Table 3**).

Multivariate logistic regression analysis and ROC analyses in terms of predicting pneumonia were also performed with the BMI Z-score, MPV, and RDW parameters that differed significantly between the groups. On the basis of multivariate logistic regression analysis, BMI Z-score [odds ratio (OR): 2,946, 95%

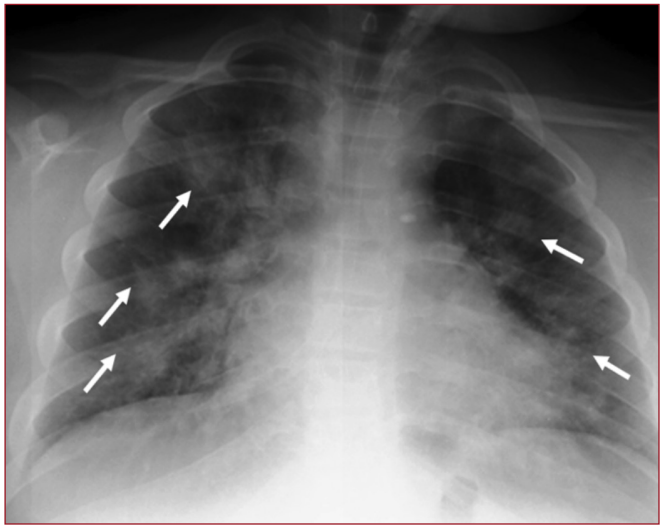

Figure 1. Posteroanterior chest X-ray showing consolidation areas (arrows) in all zones in the bilateral pulmonary parenchyma in a 10-year-old girl

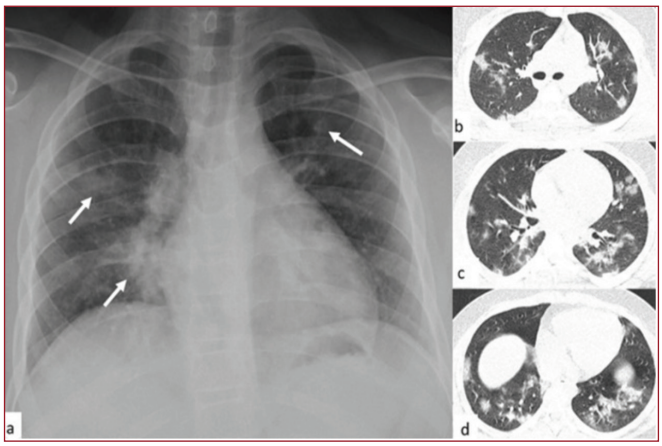

Figure 2. Posteroanterior chest X-ray and non-contrast axial CT section parenchymal window in a 15-year-old boy: Diffuse peripheral and peribronchovascular ground glass and consolidation areas in all zones of the bilateral parenchyma at lung-X-ray (a, arrow), and in the upper lobes (b), and in the middle lobe of the right lung and bilateral lower lobes (c, d) at computed tomography

CT; Computed tomography

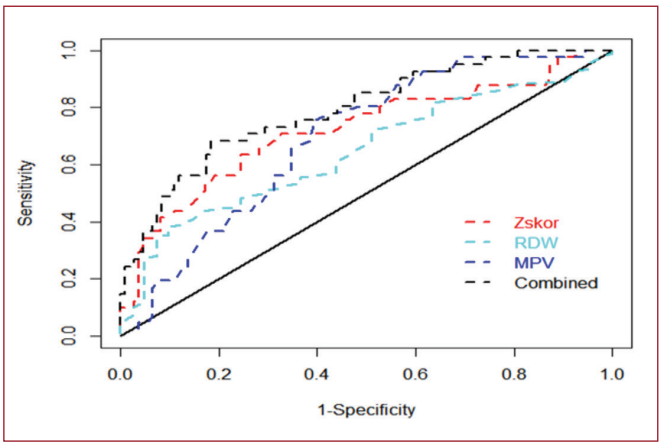

Figure 3. Receiver-operating characteristic curve for body mass index (BMI) Z Z-score, red cell distribution width (RDW), MPV and combined (MPV, RDW, BMI Z-score) parameters in the prediction of pneumonia in patients with Coronavirus Disease of 2019

MPV; Mean platelet volume, RDW; Red blood cell distribution width, BMI; Body mass index

Table 1.
Demographic, anthropometric and clinical characteristics of COVID-19 patients with pneumonia and COVID-19 patients without pneumonia

Covıd-19					
	Pneumonia-negative		Pneumonia-positive		
Variables	**n (110)**	**Median (IQR)**	**n (41)**	**Median (IQR)**	**p value**
Age (months)		60 (1-204)		120 (2-204)	0.11*
BMI		51 (3-95)		74 (6-100)	**0.00***
BMI Z-score		0.03 (-3.0-1.6)		0.6 (-1.5-3.5)	**0.00***
Hospitalization		4 (1-22)		5 (2-14)	0.14*
Gender					
Male	68		25		0.92**
Female	42		16		

*Data incompatible with normal distribution. Wilcoxon rank sum test was applied as the statistical technique, the results being expressed as median (IQR)
**The Pearson chi-square test was used in the analysis of categorical variables at two independent group analysis
IQR; Inter quantile range, BMI; Body mass index

Table 2.
Comparison of hematological parameters of COVID-19 patients with pneumonia and COVID-19 patients without pneumonia

Covıd-19					
	Pneumonia-negative		Pneumonia-positive		
Variables	**n (110)**	**Median (min.-max.)**	**n (41)**	**Median (min.-max)**	**p value**
WBC (x10^3/L)		6.56 (1.1-26.8)		6.96 (2.99-17.77)	0.85
Neutrophils (x10^3/L)		2.57 (0.27-11.3)		3.16 (0.67-15.3)	0.14
Lymphocytes (x10^3/L)		2.4 (0.54-14.5)		2.06 (0.58-7.8)	**0.043**
Hemoglobin (g/dL)		13 (8.5-18.6)		13 (10.1-19.3)	0.26
Hematocrit (%)		38 (28-62)		38 (29-66)	0.64
MCV (fl)		79 (75-101)		80 (77-101)	0.19
RDW (%)		13.1 (11.1-37.1)		12.6 (11.4-16.9)	**0.005**
PLT (x10^3/L)		299 (83.2-880)		292 (156-880)	0.96
MPV (fl)		10.2 (5.3-17.7)		11.1 (6.5-17.1)	**0.0002**
PCT (%)		0.23 (0.1-0.79)		0.26 (0.1-0.53)	0.68
PDW (%)		16.8 (8-18.60)		16.9 (15.6-18.6)	0.25
NLR (%)		1.1 (0.004-10.36)		1.6 (0.1-12.4)	**0.021**
PLR (%)		0.11 (0.01-0.59)		0.14 (0.02-0.56)	**0.027**

*Values are median (min.-max), p value obtained via Mann Withney-U test
WBC; White blood cell, MCV; Mean corpuscular volume, RDW; Red blood cell distribution width, PLT; Platelet, MPV; Mean platelet volume, PCT; Procalcitonin, PDW; Platelet distribution width, NLR; Neutrophil-lymphocyte ratio, PLR; Platelet-lymphocyte ratio, Min.-max; Minimum-maximum

Table 3.
Comparison of biochemical parameters of COVID-19 patients with pneumonia and without pneumonia

Covıd-19					
	Pneumonia-negative		Pneumonia-positive		
Variables	**n (110)**	**Median (min.- max.)**	**n (41)**	**Median (min.-max)**	**p value**
CRP (mg/dL)*		0.7 (0.1-96)		2.31 (0.1-160)	0.24
LDH (U/L)*		260 (150-625)		311 (143-726)	0.18
D-dimer (mg/L)*		0.40 (0.16-11)		0.5 (0.19-8.86)	**0.01**
AST (U/L)*		30 (9-214)		32 (12-77)	0.92
ALT (U/L)*		18 (6-94)		18 (7-179)	0.50
Urea (mg/dL)*		21 (4-50)		19 (9-39)	0.74
Creatinine (mg/dL)**		0.53 (±0.12)		0.57 (±0.14)	0.08
Glucose (mg/dL)*		91 (57-149)		95 (69-148)	0.21
Ferritin* (µg/L)		32 (4.6-794)		42 (5.7-820)	0.12
Sedimentation*(mm/h)		13 (1-32)		15 (2-51)	0.05
CK* (U/L)		97 (18-4,267)		86 (29-701)	0.15

*: Values are median (min.-max.), P value obtained via Mann Withney-U test
**: Values are mean ± SD, P value obtained via t-test
CRP; C-reactive protein, LDH; Lactate dehydrogenase, CK; Creatine kinase, Min.- max.; Minimum-maximum

confidence interval (CI): 1.701-5.668, p=0.00), MPV (OR: 1.219, 95% CI: 1.026-1.461, p=0,001), and RDW (OR: 0.617, 95% CI: 0.429-0.835, p=0.001) were independent risk factors of pneumonia in patients with COVID-19. ROC curve analysis showed that the AUC of MPV in group pneumonia was 0.694 (95% CI: 0.607-0.782), with the diagnostic sensitivity 75.60% and specificity 60.55%; AUC of BMI-Z score was 0.721 (95% CI: 0.621-0.821), with sensitivity 63% and specificity 75%; AUC of RDW was 0.646 (95% CI: 0.554-0.739), with sensitivity 81% and specificity 90%; AUC of BMI-Z score, RDW combined with MPV

was 0.792 (95% CI: 0.71-0.874), with the diagnostic sensitivity 95.40% and specificity 80%. The optimal cut-off values for the MPV, BMI-Z score and RDW and to be able to differentiate pneumonia patients were 10.5, 0.42 and 14.2, respectively. (**Figure 3**)

Discussion

COVID-19 infection is generally milder in children. This may be due to the lower social isolation, frequencies of comorbidity, and low smoking rates among children compared to adults, together with their greater pulmonary regeneration capacity and lower angiotensin converting enzyme expression[11]. A study involving 2,143 children in China reported that severe and critical cases were observed at rates of 10.6% in patients aged under one year, 7.3% in those aged 1-5 years, 4.3% in those aged 6-10, 4.1% in those aged 11-15, and 3% in children aged over 16[12]. Pulmonary involvement can be detected in most children hospitalized for follow-up. Pneumonia was detected in 81 (65.8%) out of 123 children who underwent CT of the lung in a study from China. Right lung involvement was observed in 17 (13%) of these 81 children, left lung involvement in 35 (28%), and bilateral pulmonary involvement in 29 (23%)[13]. In the present study, pulmonary involvement was detected in 41 (27.1%) patients assessed by means of chest X-ray and/or CT. Bilateral peripheral predominant multifocal involvement and consolidation areas were present in 19 (46.35%) of these patients. Moreover when patients who had undergone pulmonary CT were considered merely, bilateral involvement was determined in six (54.5%) of these patients Chest CT has a important for diagnosis of COVID-19. Most children with COVID-19 experience mild illness. Pulmonary involvement on CT is often less extensive than in adults[14]. For these reasons, in order to balance the risk of radiation and necessity for chest CT, we performed chest CT in selected patients who had had increased breath rate with a blood oxygen saturation at rest < 92% or those with disease progression during hospitalization[15].

Performing early risk stratification by evaluating abnormal clinical findings and laboratory findings together in COVID-19 patients will enable at risk of respiratory failure, multiple organ failure, and even death[16]. Indeed, BMI Z-score, MPV, NLR, PLR, and D-dimer levels were significantly higher in patients with pneumonia. While there was no significant difference between the patient groups in terms of CRP, LDH and ferritin levels, mean CRP, LDH and ferritin levels were found to be higher in patients with pneumonia. Based on our multivariate logistic regression analysis results, we found that BMI Z-score, MPV, and RDW were independent risk factors for pneumonia in COVID-19 patients. Obesity exacerbates the risk of serious COVID-19 in children. The impaired pulmonary functions in obesity, immune and thrombogenic responses to pathogens are also compromised[17]. One multicenter study reported a high rate of obesity among children hospitalized due to COVID-19[18]. In this study, BMI Z-scores were significantly higher in patients with pneumonia. A positive correlation was observed between BMI Z-score and inflammatory markers. We think that obesity increases the severity of inflammation and induces disease progression in children patients with COVID-19. Several studies have reported that hematological markers, the peripheral blood levels of cytokines, and coagulation parameters such as CRP, neutrophil count, D-dimer, NLR, and PLR increase considerably in contrast with T lymphocytes in severe forms of COVID-19[19].

However, the majority of laboratory data in COVID-19-associated pediatric patients comes from case reports or a small number of observational studies. The most frequently reported coagulation/fibrinolytic abnormality associated with COVID-19 is an increase in D-dimer levels[20]. D-dimer is a cross-linked fibrin degradation product produced when plasmin breaks down fibrin to break up clots. D-dimer reflects the functioning normally of coagulation and fibrinolysis systems[21]. Recent studies have reported that severity of the disease and prognosis are associated with D-dimer level elevation in patients hospitalized due to severe COVID-19[22].

COVID-19, infection of bone marrow increased platelet breakdown due to immune system activation, and greater platelet accumulation in the lungs leads to thrombocytopenia[23]. A decreased platelet count increases platelet production and the proportion of more functionally active young platelets. MPV rises as a result. It has been found that there is an increase in MPV values in severe COVID-19 patients, particularly those with risk of mortality[24]. A study involving adult patients with COVID-19 reported that a one-unit increase in MPV resulted in a 1.76-fold increase in the risk of mortality[25]. Similarly in this study, MPV values were significantly higher in patients with COVID-19-associated pneumonia. We suggest that the higher levels of D-dimer together with higher values of MPV and LDH might be highlighting the possibility of more obvious activation of the coagulation system induced by prominent inflammatory responses and dysfunction of endothelial cells in patients with pneumonia in our study. RDW indicates heterogeneity in size of erythrocytes and anisocytosis in red blood cells. Anisocytosis may present with impaired erythropoiesis in inflammation-related diseases and renal dysfunction with insufficient erythropoietin production[26].

An association between increased mortality in COVID-19 patients and decreased RDW levels has been reported[27]. Low RDW values have been reported in COVID-19 patients with severe pneumonia, while RDW levels increase together with improvement[28]. In this study, RDW was significantly lower in patients without pneumonia, but the mean RDW values of both groups were within normal limits. This finding, which emerged in our study, may indicate that the severity of inflammation did not increase at a level that would affect RDW in patients with pneumonia. Due to the cross-sectional and single-center nature of this study, the small number of patients in the groups, and the fact that the number of patients without pneumonia was 2.68 times higher than that of those with pneumonia, the lower mean RDW value in patients with pneumonia should be interpreted with caution. We did not study procalcitonin levels, a potential marker of secondary bacterial infection in patients included in this study. Hence, the higher levels

of inflammatory markers in patients with pneumonia might have been partially related to secondary bacterial infections.

Conclusion

The current study showed higher levels of inflammatory, coagulation and hematological parameters in patients with COVID-19 presenting with pneumonia. We suggest that BMI-Z score and MPV value may assist in predicting pulmonary involvement in patients with COVID-19.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

Conflict of Interest: There are no conflicts of interest in connection with this paper, and the material described is not under publication or consideration for publication elsewhere.

Ethics Committee Approval: The study was carried out with the permission of Bolu Abant İzzet Baysal University Clinical Researches Ethics Committee Clinical Researches (Decision no: 208, Date: 27.07.2021).

Financial Disclosure: The authors have no conflicts of interest to declare.

Informed Consent: No conflict of interest was declared by the authors.

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Journal of Pediatric Academy

Original Article

Year: 2023 Volume: 4 Issue: 1
Doi: 10.4274/jpea.2023.199
J Pediatr Acad 2023; 4: 18-24

Assessment of Hypertension in Children with Autosomal Dominant Polycystic Kidney Disease; Single-Center Experience

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Article Information

Article Type: Original Articles
Article Group: Pediatric Rheumatology

Received: 02.11.2022
Accepted: 01.01.2023
Available Online: 31.03.2023

Cite this article as: *Uygun A, Nalçacıoğlu H, Aydoğ Ö. Assessment of Hypertension in Children with Autosomal Dominant Polycystic Kidney Disease; Single-Center Experience. J Pediatr Acad 2023; 4: 18-24*

Abstract

Autosomal dominant polycystic kidney disease (ADPKD) is one of the most common hereditary renal cystic diseases. Although its clinical manifestations usually occur in adulthood, hypertension (HT) is known to develop in most patients before the decline in renal function and it is associated with faster progression to end stage kidney disease (ESKD). We investigated ambulatory blood pressure monitoring (ABPM) results of 23 patients with ADPKD, followed up in the Pediatric Nephrology Clinic of Ondokuz Mayıs University Medical Faculty Hospital. Patients' demographic characteristics, laboratory and ultrasonography (US) results, office blood pressure, and ABPM measurements were evaluated. The parameters of gender, age, increased kidney size, proteinuria, glomerular filtration rate (GFR) was compared in hypertensive and non-hypertensive group. Twenty three patients (13 girls, ten boys) with a mean age of 11.94±4.01 (min-max: 4.6-18) years and a female/male ratio of 1.3/1 were examined. Ultrasound revealed increased kidney sizes in 12 patients (52.2%) and multiple cysts in the bilateral kidneys in 20 patients (87%). Mild to moderate proteinuria was detected in 7 patients (30.4%). The HT ratio of patients was 52.2% and 39.1% when assessed with office blood pressure (BP) measurement and ABPM respectively. A non-dipper pattern was established in 14 patients (60.9%). Gender, age, increased kidney size, proteinuria, GFR did not differ significantly between ADPKD patients with and without ambulatory HT. This study shows that nearly half of children with ADPKD have HT by ABPM. BP should be regularly screened by ABPM in all pediatric ADPKD patients.

Keywords: Ambulatory blood pressure monitoring, autosomal dominant polycystic kidney disease, childhood, hypertension, kidney disease

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Introduction

Autosomal dominant polycystic kidney disease (ADPKD) is one of the most common hereditary cystic disease characterized by the progressive development of kidney cysts resulting in kidney enlargement and decline in renal function with developing end-stage kidney disease (ESKD).[1-3] Although ADPKD seems to be a kidney-specific disorder, it is a multisystem hereditary disease with cyst formation in other organs, primarily the liver and pancreas, and associated with cardiovascular abnormalities.[3-5]

Highlights

- Hypertension, ambulatory blood pressure measurement, autosomal dominant polycystic kidney disease.

Early identifying the risk factors which is associated with more rapidly progression to ESKD remains the base of the management of ADPKD. Male sex, *Polycystic kidney disease 1* (*PKD1*) gene, episodes of hematuria, and hypertension (HT) play a vigorous role in the progression of renal disease to ESKD.[2,3,5-7] In children with ADPKD, HT affects 10-35% of children, associated with cardiovascular disease and decline in glomerular filtration rate (GFR) over time.[6-11]

In this study, we investigated the demographic characteristics, clinical findings, and blood pressure (BP) values using office and ambulatory monitoring in children diagnosed with ADPKD.

Material and Method

This single-centre, observational study was conducted at the Pediatric Nephrology Division at Ondokuz Mayıs University. A total of 23 children with an diagnosis of ADPKD who had undergone an ambulatory blood pressure monitoring (ABPM) were recruited. The inclusion criteria were:

- Diagnosis of ADPKD adequate diagnostic criteria would be considered as based on positive family history of ADPKD in a parent combined with the presence of at least two kidney cysts,[10] unknown family history case, a patient with bilaterally enlarged kidneys and innumerable cysts, without other findings to suggest a different cystic disease, most likely has ADPKD,
- ≥2 visits in our pediatric nephrology center,
- Fully completed laboratory and clinical investigation (kidney ultrasound, clinic blood pressure, urinalysis, and serum creatinine).

In total, 23 children were included in the study. The median time of follow-up was 5.6 years (min-max: 2-14).

The Ondokuz Mayıs University Clinical Research Ethics Committee approved this study (27.12.2019 with the decision number OMÜ KAEK 2019/879). Informed consent was obtained from parents and children for patients aged 11-18 years and from parents only for those ten years of age and under.

Demographic data, physical examination findings, laboratory and ultrasonography (US) examinations were accessed from the patient registry system. The presence of parental consanguinity, a family history of cystic kidney disease, and whether undergoing dialysis were reached from the patient files. The US of the abdomen evaluated kidney and liver sizes, parenchyma echogenicity, cyst number, and cyst sizes. Urine collected over 24h for quantitative measurement of protein. If protein excretion was <4 mg/m^2/hour, 4-40 mg/m^2/hour, and >40 mg/m^2/hour, it was considered normal, mild-moderate proteinuria, and nephrotic (massive) proteinuria, respectively. GFR values of the patients were calculated by the 24-hour creatinine clearance method. A mercury sphygmomanometer measured clinic office BP. After the patient had rested for at least 10 minutes in a sitting position, at least three measurement values were obtained at different times with an appropriately sized sleeve attached to the right arm. Calculated mean systolic and diastolic BP values were evaluated based on the 2017 American Academy of Pediatrics guidelines for childhood HT.[12] According to the guideline, HT was defined as systolic and diastolic BP ≥95 the percentile. ABPM was performed on all children with a Physio-Port Up brand device. As long as the machine was attached, our patients were asked to keep a diary and record hours of sleeping, eating, stressing, exercising, and studying. By attaching a cuff to the patient's non-dominant arm, ABPM reports, where measurements were made every 20 minutes during the day and every 30 minutes at night and at least 40 valid measurements were recorded, were evaluated. Daily, night (sleep), and day (wakefulness) mean, minimum and maximum systolic and diastolic BP values, night, and day mean arterial BP values, and daily, night, and day BP loads (Calculation of the BP values above the 95th percentile as percentages of all measurements) were obtained automatically from the computer data. ABPM results were evaluated according to the report, where the daily, day, and night average arterial pressure mean arteriel blood pressure (MABP) measurements were obtained with ABPM out of 1,000 Central European children, updated by American Heart Association in 2014 and published by Anti Müllerian Hormone in 2016.[13,14]

Patients who had daily, day, or night MABP values >95th percentile with ABPM and systolic and/or diastolic BP load >25th percentile were considered ambulatory HT. Patients who had mean arterial BP values <95th percentile with ABPM and systolic and/or diastolic BP load >25th percentile were accepted as prehypertension. In the office measurements, patients with a mean systolic and/or diastolic BP >95th percentile and diagnosed with HT, but those who had mean arterial BP values >95th percentile with ABPM and systolic and/or diastolic BP load <25th percentile were considered to have white coat HT. The 10-15% decline in night (sleep) measurements compared to daytime (wakefulness) measurements with ABPM was considered "dipper pattern," less than 10% decline "non-dipper pattern," and more than 20% decline "forward-dipper pattern."[13]

Statistical Analysis

Analyses were done using Statistical Package for the Social Sciences 22.0 (SPSS IBM Corp, Armonk, New York, USA). The compatibility of variables was

investigated using the analytic (Shapiro-Wilk) test. The characteristics of patients were determined using descriptive statistics. Parameters compatible with normal distribution were defined as mean standard deviations, and parameters that did not fit normal distribution were described as medium and distribution (lower-upper limit). The comparisons of proportions were performed with the chi-square tests. For the comparisons between the groups, the independent samples t-test was used for the parameters with normal distribution, and the Mann-Whitney U-test was used for the parameters with non-normal distribution. P<0.05 is considered to be statistically significant.

Results

Demographic Characteristics

The mean age of the study group was 11.94±4.01 (min-max: 4.6-18), years of which 13 (56.5%) were female, and 10 (43.5%) were male. The mean follow-up period of the patients was 5.67±2.79 (min-max: 2-14) years. The median age at diagnosis was 5.1 (6 months -14.2 years). There was consanguinity between the parents in only one of the 23 patients (4.3%). While a family history of cystic kidney disease was present in 17 patients (73.9%), it was not present in 6 patients (26.1%). The family history was positive on the mother's side in 8 patients, on the father's side in 6, on their siblings in 2, and both on the mother's and father's side in a patient whose parents were relatives. A total of 9 patients (39.1%) in their family histories had at least a relative who developed end stage renal disease (ESRD) and underwent dialysis; these patients had a positive family history on the mother's side in 3 patients and on the father's side in 6 patients. Demographic and clinical features of the patients were shown in **Table 1**.

US Findings

The mean right kidney vertical length of the patients was 107,09±20.9 (min-max: 80-160) mm, mean left kidney vertical length was 109,43±24.09 (min-max: 80-170) mm. Patients' mean renal vertical length standard deviation score (SDS) was calculated as 1.40±2.65 mm for the right kidney and 1.69±2.99 mm for the left kidney. Twelve of the patients (52.2%) had an increase in kidney sizes; 20 (87%) and 3 (13%) had multiple cysts and two or fewer cysts, respectively, in the bilateral kidneys. The diameter of the largest cyst detected in the patients was calculated as 21±14.05 mm. Extrarenal cysts located in the liver were found in only one patient (4.3%); none of the patients had stones in the urinary system. The largest cyst size of 20 patients was determined as 20.65±13.67 mm, while the largest cyst length of 12 patients was 21±14.05 mm (**Table 2**).

Laboratory Findings

The mean total leukocyte count, hemoglobin value, and platelet count were found to be 6844,09±1523,8 (min-max: 4,970-11,190)/mm^3, 13.1±1.43 (min-max: 9.7-16.1) g/dL, and 280,363±64,727 (min-max: 168,000-421,000)/mm^3, respectively. The mean blood urea nitrogen, serum creatinine, GFR, plasma sodium, plasma potassium, serum calcium, serum phosphorus, and serum albumin values of the patients were observed as 12.40±3.97 (min-max: 8.3-22) mg/dL, 0.59±0.2 (min-max: 0.32 -1.16) mg/dL, 126,71±40.94 (min-max: 40.65-196,50) mL/minute/1.73 m², 140,48±2.31 (min-max: 136-146) [miliEkivalan (mEq)/L], 4.41±0.29 (min-max: 3.8-4.9) mEq/L, 9.91±0.34 (min-max: 9.2-10.8) mg/dL, 4.25±0.60 (min-max: 3.26-5.47) mg/dL, and 4.73±0.26 (min-max: 4.2-5.18) gr/dL, respectively. Liver function tests of all patients were detected to be normal. The mean spot urine protein-creatinine ratios of the patients were measured as 0.23±0.50 (min-max: 0.03-1.33); this ratio was greater than 0.2 in only one patient. 24-hour urine was collected in 22 patients, accordingly, daily protein excretion in urine was calculated as the mean 3.22±1.57 (min-max: 0.99-7.32) mg/m²/hour; while 15 patients (65.2%) had no proteinuria, 7 patients (30.4%) had mild proteinuria. Microalbumin excretion in 24-hour urine of the patients was measured as the mean 24.22±34.39 (min-max: 10-124) mg/day; while there was no microalbuminuria in 16 patients (69.9%), microalbuminuria was detected in 6 patients (26.1%) **Table 2** showed the US and laboratory data of the patients.

Table 1.
Demographic and clinical features of the patients with ADPKD

General Features	Value
No of patients (boys/girls)	23 (10/13)
Age, mean ± SD, year	11.94±4.01
Family history, n (%)	17 (73.9)
Affected mother, n (%)	8 (47)
Family history of ESRD, n (%)	9 (39.1%)
Duration of follow-up, mean ± SD, year	5.67±2.79

ADPKD; Autosomal dominant polycystic kidney disease, SD; Standard deviation, ESRD; End stage renal disease

Table 2.
Radiological and laboratory data of the patients with ADPKD

Data	Value
Radiological findings in admission	
Right kidney size, SDS median (min-max)	1.36 (-1.78 -8.65)
Left kidney size, SDS median (min-max)	1.10 (-1.56 -9.92)
Enlarged kidneys, n (%)	12 (52.2)
Renal cyst size, median (min-max) mm	19 (5- 58)
Bilateral renal cyst, n (%)	20 (87)
Bilateral >4 cysts	20 (87)
Urolithiasis/cyst wall calcification	
Laboratory findings in admission mean ± SD	
Hemoglobin (g/dL)	13.1±1.43
Leukocyte, × 10^3/mm^3	6844,09±1523,8
Platelets, × 10^3/mm^3	280.363±64727
Creatinine (mg/dL)	0.59±0.2
GFR, mL/min/1.73 m^2	126,71±40.94
GFR ≥140 mL/min/1.73 m^2, n (%)	9 (39.1)
Proteinuria, n (%)	7 (30.4)

ADPKD; Autosomal dominant polycystic kidney disease, SDS; Standard deviation score, SD; Standard deviation, GFR; Glomerular filtration rate

Office BP Measurements

The mean systolic BP, diastolic BP, and heart rate were found to be 118,83±16.55 millimeters of mercury (mmHg), 80.87±15.88 mmHg, and 101,61±26.02 respectively. Eight patients (34.8%) were considered normotensive, 3 patients (13%) prehypertensive, and 12 patients (52.2%) hypertensive. Of the 12 hypertensive patients, 6 were girls, and 6 were boys; when HT was staged, 5 (41.7%) were classified as stage 1 HT, 7 (58.3%) as stage 2 HT.

Ambulatory BP Measurements

Patients whose more than 90% of the measurements were appropriate were included in the study. **Table 3** summarizes the office and ABPM data. The mean systolic and diastolic BP was 108,48±8.27, 69.22±7 mmHg, respectively. In the daytime measurements, the mean systolic BP was 109,83±7.20, while its minimum and maximum values were 78.70±6.81 and 153,87±15.13 mmHg. Besides, the mean diastolic BP was 71.26±6.54; its minimum and maximum values appeared to be 43.30±5.06 mmHg and 111,30±11.83 mmHg. During night measurements of patients, while the mean systolic BP was 104,09±12.73, its minimum and maximum values were 85.22±12.25 mmHg and 130,13±21.13 mmHg. The mean diastolic BP was 62.22±9.20; its minimum and maximum values were detected 44.87±7.75 mmHg ve 87.30±17.41 mmHg. Considering ABPM measurements; nine patients (39.1%) were diagnosed with ambulatory HT, four patients (17.4%) prehypertension, and one patient (4.3%) white coat HT. Two of 5 patients with stage 1 HT in the office measurement were diagnosed as HT with ABPM, two as prehypertension, and one as white coat HT. Fourteen of the patients (60.9%) had a non-dipper pattern and ten of the patients (43.4%) had isolated nocturnal HT (**Table 3**).

Patients with and without ambulatory HT were compared in terms of gender, age, increase in kidney size, 24-hour urinary protein excretion, kidney size SDS, and GFR values. No statistical difference was detected

Table 3.
Blood pressure measurement data and stage of hypertensive patients with ADPKD

	Data	Value
Office blood pressure	Systolic blood pressure, mean ± SD, mmHg	118,83±16.55
	Diastolic blood pressure, mean ± SD, mmHg	80.87±15.88
	Heart rate mean ± SD, /min	101,61±26.02
	Stage of hypertension, n (%)	15 (65.2)
	Pre-hypertensive	3 (13)
	Hypertensive	12 (52.2)
Ambulatory blood pressure	Daytime systolic BP, mean ± SD, mmHg	109,83±7.20
	Daytime systolic BP, SDS	-0.7 (-2.36 -3)
	Daytime diastolic BP, mean ± SD, mmHg	71.26±6.54
	Daytime diastolic BP, SDS	-0.29 (-1.87 -3.49)
	Nighttime systolic BP, mean ± SD, mmHg	104,09±12.73
	Nighttime systolic BP, SDS	0.51 (-1.72-5.16)
	Nighttime diastolic BP, mean ± SD, mmHg	62.22±9.20
	Nightime diastolic BP, SDS	1.11 (-1.57-5.08)
	Systolic HT, n (%)	4 (17.4)
	Diastolic HT, n (%)	9 (39.1)
	Stage of hypertension, n (%)	
	Pre-hypertensive	4 (17.4)
	Hypertensive	9 (39.1)
	Non-dipper patern	14 (60.9)
	Isolated nocturnal hypertensive	10 (43.4)

ADPKD; Autosomal dominant polycystic kidney disease, SD; Standard deviation, mmHg; Millimeters of mercury, BP; Blood pressure, SDS; Standard deviation score, HT; Hypertension

Table 4.
Comparision of hypertensive and non-hypertensive ADPKD patients

Data	Hypertension present (+)	Hypertension absent (-)	p
Number of patients Sex (female/male)	6/3	7/7	0.43
Age, years	11.03± 4.35	12.53±3.83	0.394
Right kidney size, SDS	2.08 (-1.78-8.65)	0.53 (-1.48-2.62)	0.159
Enlarged kidneys, number of patients	6	6	0.265
24 hour urine protein excretion (mg/m^2/hour)	4.03 ±1.85	2.76±1.23	0.068
GFR, mL/min/1.73 m^2	124.6±47.3	127.7±39.2	0.873

ADPKD; Autosomal dominant polycystic kidney disease, SDS; Standard deviation score, GFR; Glomerular filtration rate

(**Table 4**), also when these two groups compared in terms of 24-hour urinary protein excretion and right kidney size SDS there are no statistical difference was found. (**Figure 1, 2**) In addition to dietary and dynamic aerobic exercise recommendations as conservative treatment, antihypertensive drug therapy was started diagnosed with prehypertension and ambulatory HT. The angiotensin-converting enzyme (ACE) inhibitor was also initiated for antiproteinuric effect in two patients with proteinuria but without HT.

Discussion

Autosomal dominant polycystic kidney disease, characterized by multiple cyst formation in the kidneys, increased kidney sizes, and progression to ESRD over time, mainly in the 5th-6th decade.[1-3] Structural changes, HT, proteinuria about 2-5% start in childhood, ranging from severe neonatal presentation to the incidental finding of kidney cysts on imaging.[2] There are limited reports of predictors of kidney disease progression in ADPKD.[8,15-20]

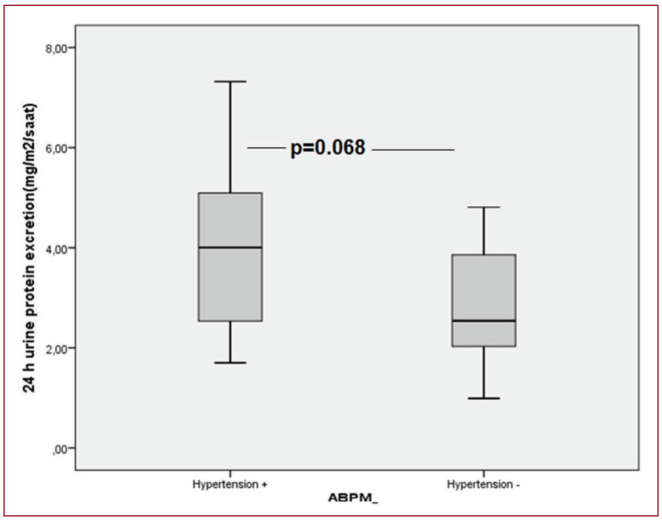

Figure 1. Comparision of 24 hour urine protein excretion in hypertensive and non hypertensive ADPKD patients.

ADPKD; Autosomal dominant polycystic kidney disease

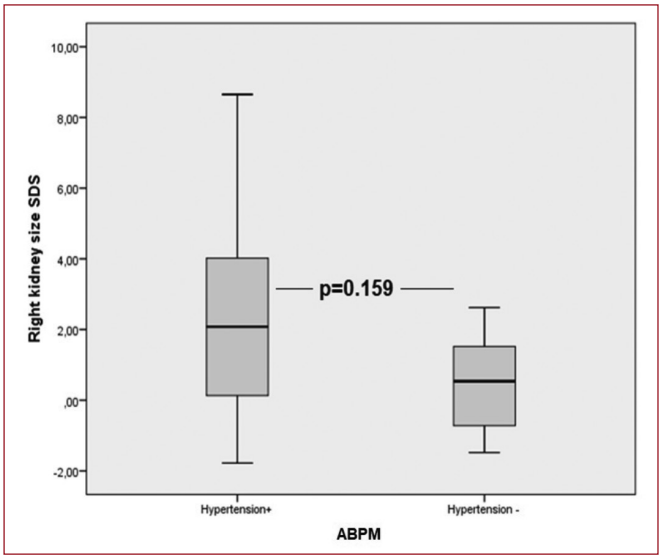

Figure 2. Comparision of right kidney size standart deviation score in hypertensive and non hypertensive ADPKD patients.

ADPKD; Autosomal dominant polycystic kidney disease

We reported 23 pediatric patients with ADPKD investigating the demographic, laboratory, radiological data, with both office and ambulatory BP measurements. Also, we compared the hypertensive /non-hypertensive patients according to the clinical predictors. Based on the studies, age at presentation is associated with the progression of kidney disease.[2,6,15] Early diagnosis of ADPKD (in utero or infancy) are more likely to develop HT, nephromegaly, or decreased GFR.[15] In this study, two patients had an early diagnosis of ADPKD, and both were hypertensive and had nephromegaly. In addition, one patient had a lower GFR; the other had a hyperfiltration of more than 140 mL/min/1.73 m^2. Hyperfiltration is the other precursor or the risk factor for ADPKD progression. In a study, children with glomerular hyperfiltration at baseline have been determined as the underlying cause of faster kidney growth and GFR decline.[20] In the current study, nine patients had glomerular hyperfiltration, HT detected in two of the nine patients.

Proteinuria is the earliest progression marker in both forms of chronic kidney disease. The presence of proteinuria has been associated with the development of HT and more severe kidney cystic disease.[10,15] An international consensus on ADPKD recommended screening proteinuria and treating ACE inhibitors or angiotensin receptor blockers (ARB) if proteinuria is present.[21] In our study, proteinuria was present in almost 30.4% of children with ADPKD similar rate of study by Fick-Brosnahan et al.[19]

HT is one of the early warning signs associated with decreased GFR over time and higher kidney volumes in patients with ADPKD. About 50-80% of adult and 27-37% of pediatric ADPKD patients have HT.[15,22,23] In our cohort, 39.1% of patients have HT, which corresponds well with the studies in children with ADPKD.[8,15,16,24] A survey by Shamshirsaz et al.[15] assessed 199 pediatric ADPKD patients according to age presentation. Forty-six children in the first 18 months were defined as very early-onset (VEO) and 153 children after 18 months as not very early-onset (non-VEO). 43% of VEO cases and 29% of non-VEO patients were found hypertensive. In the VEO group, this frequency increased up to 52% during the follow-up. Seeman et al.[8] reported that ambulatory HT is present in 35% of children with ADPKD. While Tee et al.[24], in their study from Canada, found the prevalence of HT in children with ADPKD to be 46%. Reed et al.[16] has shown that HT is associated with kidney size and the number of kidney cysts in children with ADPKD. We found no significant change in kidney growth or presence of proteinuria in the hypertensive group. ABPM was performed in all children with ADPKD in our center, a more sensitive form of BP measurement. 39.1% of patients have ambulatory HT, of whom 14 patients had a non-dipper pattern, and three had isolated nocturnal HT.

In different studies, HT has been reported to appear in the non-dipper pattern, disrupting the circadian rhythm in ADPKD.[23-25] Nocturnal HT is also prevalent in children with ADPKD. In a study of 310 children, 52% of the patients had non-dipper, and 18% had isolated nocturnal HT.[23] Another study in patients with ADPKD

has also pointed out an association between BP and renal size. Early initiation of HT might relate to bilateral renal ischemia developed secondary to cyst altering the renal vasculature leading to increased kidney size.[8,18,19,22] There is a significant correlation between kidney length and both daytime and nighttime blood pressure.[8] In contrast to studies, we failed to observe any meaningful relationship between HT and renal function or increased kidney size.

Due to potential kidney protective effects, antihypertensive therapy using ACE inhibitors and ARB blockers might retard the progression of ADPKD.[26,27] Another study by Schrier et al.[22] found that close BP control (<90p) was associated with slower kidney growth, improved left ventricular mass index, and lower proteinuria. However, a study in children with hypertensive ADPKD found no effect on kidney growth under the ACE inhibitor over five years. Still, it showed a potential impact on preventing an increase in left ventricular mass index and loss of renal function in patients with borderline HT (75th to 95th percentile).[10] Therefore, as well as the dietary and dynamic aerobic exercise recommendations, the ACE inhibitor was started on 14 patients (60.9%) with pre-HT and HT with ABPM in the current study.

The limitations are mainly the retrospective design, the lack of kidney volume measurement, and the long-term follow-up. On the other hand, the strengths of this study are the relatively large number of patients in a single center, and ABPM was evaluated in all patients. Therefore, we would recommend a longitudinal survey using ABPM in children with ADPKD and follow up the long term of ACE inhibitor on kidney growth and renal survival.

Conclusions

This study has shown that children with ADPKD suffer from HT with a rate of 39.1% by ABPM. Our study results point out HT that starts at younger ages in children with ADPKD. We can conclude that HT should be regularly screened in all pediatric ADPKD patients.

Author Contributions: Uygun A: 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. Nalçacıoğlu H: Planning methodology to reach the conclusions, taking responsibility in the writing of the whole or important parts of the study. Aydoğ O: Constructing the hypothesis or idea of research and/or article, taking responsibility in logical interpretation and conclusion of the results, reviewing the article before submission scientifically besides spelling and grammar.

Conflict of Interest: On behalf of all authors, the corresponding author states that there is no conflict of interest. This study was presented as an oral presentation in the 64th Turkish National Pediatric Congress, December 2020.

Ethics Committee Approval: The study was conducted in accordance with the Declaration of Helsinki and approved by the Clinical Research Ethics Committee of Ondokuz Mayıs University (27.12.2019 with the decision number 2019/879).

Financial Disclosure: The authors have no conflicts of interest to declare.

Informed Consent: Informed consent was obtained from the parents of the patients.

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Journal of Pediatric Academy

Original Article

Year: 2023 Volume: 4 Issue: 1
Doi: 10.4274/jpea.2023.198
J Pediatr Acad 2023; 4: 25-32

The Relationship Between Dyspnea Severity with Radiological and Laboratory Findings in Pneumonia in Children in Pediatric Palliative Care

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Article Information

Article Type: Original Articles
Article Group: Pediatric Rheumatology

Received: 02.11.2022
Accepted: 24.01.2023
Available Online: 31.03.2023

Cite this article as: *Harputluoğlu N, Coşkun M, Çubukçu D, Çelik T. The Relationship Between Dyspnea Severity with Radiological and Laboratory Findings in Pneumonia in Children in Pediatric Palliative Care. J Pediatr Acad 2023; 4: 25-32*

Abstract

In care patients; pneumonia is common due to being bedridden, atrophy of respiratory muscles and use of medical devices. Dyspnea is the second most common symptom after pain in pediatric palliative care. In this study, it was aimed to examine the relationship between the severity of dyspnea and pneumonia. The study is a study that included patients admitted to pediatric palliative care, diagnosed with pneumonia, and applied Modified Borg Scale (MBS) between December 15, 2019 and December 15, 2020. The MBS has a scoring system ranging from 0 to 10 and assesses the severity of dyspnea. A total of 72 (34.4%) patients diagnosed with pneumonia and underwent MBS were included in the study. 51.4% (n=37) of the study group were male, and the median age was 6.00 years (ranges of quarters=9). It was observed that the severity of dyspnea did not affect determining the pneumonia type and possible pathogen (p=0.613, p=0.948, respectively) In line with the results of the study, it can be concluded that there is no relationship between the severity of dyspnea and pneumonia in patients in need of care.

Keywords: Pneumonia, pediatric palliative care, severity of dyspnea

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Introduction

Pneumonia ranks among the top in admission to pediatric emergency departments, clinic wards, and intensive care units and is one of the leading causes of morbidity and mortality in children globally.[1,2] The World Health Organization reports that pneumonia is the most common cause of death in children under the age of five worldwide. Although pneumonia-related deaths have decreased somewhat with safe, effective, and cost-effective treatment, they still account for approximately one-fifth of child deaths globally.[3] Pneumonia, the acute inflammation of the lung parenchyma that usually occurs in response to infectious causes such as bacteria and viruses, is a clinical picture in which fever, respiratory symptoms, and parenchymal involvement are defined by physical examination and/or chest X-rays.[4] Risk factors include poor hygiene, low socioeconomic status, lack or insufficiency of vaccinations, and infrastructure problems in living conditions. In care patients, being bedridden, atrophy of respiratory muscles, and using medical devices are also among the risk factors for pneumonia.

Highlights

- Dyspnea is a multidimensional symptom and requires different management strategies according to its causes. The relationship between pneumonia-related dyspnea and/or severity of dyspnea and the presence of pneumonia has not been adequately studied, particularly in pediatric palliative care patients.
- The Modified Borg Scale is a scale used to evaluate dyspnea in nonverbal children. Modified Borg Scale is not related to the type of pneumonia, possible pathogens, chest X-ray and laboratory findings.
- For dyspnea, which is common in pediatric palliative care patients, causes other than pneumonia should be investigated and treatment should be given for its etiology.

Dyspnea is defined as performing the work of breathing quickly or with difficulty. Dyspnea is a common symptom in pediatric palliative care. It is the second most common symptom after pain, especially in the last month of life.[5-11] The frequency of dyspnea in pediatric palliative care has been reported to be between 17-80%, and the frequency varies according to the diagnosis and evaluation method.[12] Acute or chronic dyspnea can be frightening for the child and the family.[13-15] Dyspnea is a multidimensional symptom and requires different management strategies according to its causes. It may occur due to causes such as infection, acidosis, fluid overload, anemia, lung metastasis, pulmonary embolism, pleural effusion, heart failure, pain, and anxiety.[16] The relationship between pneumonia-related dyspnea and/or severity of dyspnea and the presence of pneumonia has not been adequately studied, especially in pediatric palliative care patients. This study aimed to examine the relationship between radiological findings and laboratory findings of the cases with the presence and severity of dyspnea followed up with the diagnosis of pneumonia in pediatric palliative care.

Material and Method

Organization of Pediatric Palliative Care (PPC) Unit

University of Health Sciences Turkey is a tertiary hospital, and the PPC center started to serve in November 2018. Our pediatric palliative care center has 12 beds and is a model of teamwork consisting of three pediatricians, eight nurses, four staff, one psychologist, one dietician, one social worker, one physiotherapist, one religious worker, and one secretary. Children with comorbidities (such as cancer, history of transplantation, and complex cyanotic congenital heart disease), potentially progressive conditions (for example, cystic fibrosis, severe immunodeficiency, muscular dystrophy), genetic disorders (such as trisomy 13, trisomy 18, osteogenesis imperfecta), and non-progressive but irreversible diseases (cerebral palsy) have been treated in our pediatric palliative care units.

Study Design

The study was cross-sectional in which patients who were followed up in pediatric palliative care between December 15, 2019, and December 15, 2020, had shortness of breath, were diagnosed with pneumonia and applied the Modified Borg Scale (MBS). The cases included in the study were clinically diagnosed with pneumonia by history and physical examination and were supported by chest X-rays and laboratory findings. Patients who did not have a cold, pharyngitis, mild fever, general condition deterioration and cases with bilateral and diffuse auscultation findings were considered as viral pneumonia. Patients with high fever, retraction, toxic appearance, and localized auscultation findings were considered bacterial pneumonia. Laboratory and radiological examinations were performed to distinguish the complexity of symptoms in patients followed in our clinic, the presence of recurrent pneumonia in bedridden patients, and other causes of respiratory distress. Chest radiographs of the patients included in the study were evaluated by a radiologist unaware of their clinical and laboratory findings. First, the presence of pneumonia was evaluated on the chest X-ray, and the involvement pattern was defined in cases with pneumonia. Because the children in our study group were non-verbal and could not evaluate themselves, the MBS was administered by a physical therapist who was unaware of X-ray and laboratory findings. The relationship between MBS scores, pneumonia pattern, and the pathogen was examined.

Data Collection Tools

Case Report Form: Sociodemographic data about the child and his/her family (child's gender, age, primary disease, medical devices and technologies used, presence of additional disease and age of the caregiver parent, gender, education, marital status, number of children, income level, employment status, and household status) was questioned with a personal information form consisting of 13 questions.

MBS: Borg Dyspnea Scale was developed by Gunnar Borg in 1982 to describe the intensity of physical activity. In 1986, the "American College of Sports Medicine" reorganized the scale by scoring between 0-10.[17] The MBS has a scoring system ranging from 0 (none) to 10 (very severe). It is accepted that the severity of dyspnea increases as the score increases on the scale without a cut-off score. (**Figure 1**) It has been used as a reliable and valid scale in various studies in our country.[18]

Radiography: Chest radiograph findings were classified as 0: Normal, 1: Lobar or focal consolidation, 2: Peribronchial reticulonodular infiltration (bronchopneumonia), 3: Ground glass infiltration, 4: Interstitial pneumonia (Linear septal thickening), and 5: Sequellae changes. Lobar and reticulonodular infiltrations were determined as bacterial pneumonia, and ground glass and interstitial infiltration as viral/atypical pneumonia.

Statistical Analysis

Statistical analysis was performed using Statistical Package for Social Sciences program version 21.0. The conformity of the variables to the normal distribution was evaluated with Kolmogorov-Smirnov and Shapiro-Wilk tests. Accordingly, it was observed that the variables were not normally distributed. Discontinuous variables were presented as numbers and percentages, and continuous variables as medians and ranges of quarters (IQR). Relationships between parameters in patients with pneumonia were evaluated with Pearson and Spearman correlation analyses. Bonferroni correction and Mann-Whitney U test evaluated MBS scores according to the presence, types, and radiological factors of pneumonia and compared bacterial and viral pneumonia characteristics. A p-value of ≤0.05 was considered statistically significant.

Results

A total of 209 patients were hospitalized during the study period, and 72 (34.4%) diagnosed with pneumonia and underwent MBS were included in the study. 51.4% (n=37) of the study group were male, and the median age was 6.00 years (IQR=9). Demographic characteristics of the cases are shown in **Table 1a**, and the characteristics of caregivers, including sociocultural characteristics, in **Table 1b**. When the primary diagnoses of pneumonia patients were examined, it was observed that 45.8% had neurological, 20.8% had genetic, 15.3% had metabolic, and 18.1% had other diseases. There was lobar pneumonia in 36.1% of the patients, bronchopneumonia in 44.4%, ground-glass appearance in 11.1%, and interstitial pneumonia in 8.3%. According to the radiological evaluation of posteroanterior chest radiography, 80.6% were bacterial, and 19.4% were viral and/or atypical pneumonia. The characteristics of the cases with bacterial and viral pneumonia are presented in **Table 2a** and **Table 2b**. When the MBS score was evaluated in the examination to determine pneumonia types and possible pathogens, it was observed that the severity of dyspnea did not affect determining the pneumonia type and possible pathogen (p=0.613, p=0.948, respectively) (**Table 3**). In patients with pneumonia, no significant relationship was found between the patient's age, laboratory findings, medical device and technological support, the presence of additional neurological diseases, such as epilepsy, length and number of hospitalizations, education and income level of the parents, the number of children cared for by the parents, the working status of the parents and

0- None
1- Very mild
2- Lightweight
3- Medium
4- A little serious
5- Serious
6- More serious
7- Very serious
8- Excess
9- Too much
10-Too much too much

Figure 1. Modified Borg Scale

Table 1a.
Demographic characteristics in patients with pneumonia

Gender **[n (%)]**	
Girl	35 (48.6%)
Boy	37 (51.4%)
Age **[median, (IQR) (1 month-18 years)]**	6.00 (9)
Number of siblings	1.50 (1)
Primary disease **[n (%)]**	
Neurological disease	33 (45.8%)
Genetic disease	15 (20.8%)
Metabolic disease	11 (15.3%)
Other	13 (18.1%)
Pneumonia type **[n (%)]**	
Lober and fokal consolidation	26 (36.1%)
Peribronchial reticulonodular	32 (44.4%)
Ground glass infiltration	8 (11.1%)
Interstitial pneumonia	6 (8.3%)
Clinical diagnose **[n (%)]**	
Bacterial	58 (80.6%)
Viral+atypical	14 (19.4%)
NC (epilepsy) **[n (%)]**	
No	19 (26.4%)
Yes	53 (73.6%)
CVS disease **[n (%)]**	
No	61 (84.7%)
Yes	11 (15.3%)
Respiratory support **[n (%)]**	
Normal	51 (70.8%)
Supported (O_2, CPAP, Home-MV)†	21 (29.2%)
Nutritional support **[n (%)]**	
Normal	17 (23.6%)
Supported (NG, gastrostomy)#	55 (76.4%)
Length of stay **[median, (IQR) day]**	20.50 (25)
Number of hospitalizations **[median, (IQR) year]**	1.00 (2)
Modified Borg Score **[median, (IQR)]**	5.50 (5)

†(O_2; Oxygen support with a mask or nasal cannula, CPAP; Continous positive airway pressure, Home-MV; Home-type mechanical ventilator), IQR; ranges of quarters, #(NG; Nasogastric tube, CVS; Cardiovascular disease, NC; Neurological comorbidity

Table 1b.
Parental characteristics of patients with pneumonia

Parent gender **[n (%)]**	
Female	66 (91.7%)
Male	6 (8.3%)
Parent age **[n (%)]**	
<30	24 (33.3%)
30-40	31 (43.1%)
>40	17 (23.6%)
Parent education **[n (%)]**	
Primary-secondary school	7 (9.7%)
High school-university	65 (90.3%)
Marital status **[n (%)]**	
Single	2 (2.8%)
Married	66 (91.7%)
Divorced-separated	4 (5.6%)
Income status* **[n (%)]**	
≤3000	35 (48.6%)
>3000	37 (51.4%)
Working status **[n (%)]**	
House-wife	58 (80.6%)
Working	14 (19.4%)
Home status **[n (%)]**	
Rent	42 (58.3%)
Own house	26 (36.1%)
With someone else	4 (5.6%)

*It is determined according to the minimum wage in our country

the MBS score (**Table 4**). Correlations determined in patients with pneumonia are presented in **Table 5**.

Discussion

The results of this study, which was performed in patients followed up with a diagnosis of pneumonia in pediatric palliative care unit, revealed that the severity of dyspnea was not related to the type of pneumonia, possible pathogens, chest X-ray and laboratory findings and that MBS was not an indicator for pneumonia.

In our country, according to the Turkey Burden of Disease Study, respiratory tract infections are responsible for 14% of all deaths in the 0-14 age group.[19] In childhood, it has been reported that 29-38% of hospitalized patients for all age groups have pneumonia.[20] Bacterial pathogens are isolated in 2-50% of cases that are followed up with the diagnosis of community-acquired pneumonia.[21,22] While viral agents are determined in 80% of children under the age of two, it is known that viral agents are rare in older children, especially between the ages of 10 and 16.[23] The present study determined pneumonia at a rate of 34.4%, similar to the literature. Pneumonia prevalence was not higher than the general population for the study group in which the patients were hospitalized due to chronic lung disease, neurological diseases, and metabolic diseases such as the pediatric palliative care service.

Dyspnea is the second most common symptom following pain in pediatric palliative care.[8] The relationship of dyspnea to pneumonia in pediatric palliative care patients and children with chronic and complex problems is unknown. Since there was no other scale developed in children in our study, MBS was used similarly to Marquis et al.[24-26] Marquis et al.[24] assigned a nurse to standardize the application of MBS in this patient population, and in our study, MBS was administered by a physical medicine and rehabilitation specialist. In the literature, the predictive value of MBS in terms of hospitalization in pulmonary hypertension was examined, but it was found that it did not predict hospitalization.[27] MBS is a marker in determining mortality associated with pulmonary hypertension in a single study.[28] While the MBS score was 0.51±1.15 at rest in children with cystic fibrosis, it was found to be 2±2.21 after exercise.[29] MBS, which was found to be 4.50±1.93 in asthmatic patients, was reported as 2.57±2.29 in the control group.[30] In our study, the MBS score was determined as 5.50 (IQR=5), indicating severe dyspnea. In patients diagnosed with pneumonia, the severity of dyspnea was not found to be related to the type and cause of pneumonia. In patients diagnosed with pneumonia, the severity of dyspnea was not found to be related to the type and cause of pneumonia. This suggested that pediatric palliative care patients experienced more severe dyspnea than children with other chronic diseases but not associated with pneumonia.

Risk factors for pneumonia include host-related causes, low socioeconomic status, crowded environments, nutritional deficiencies, poor hygiene conditions, and inadequate infrastructure in living areas. Insufficient cough reflex and respiratory muscles make it difficult to clear airway secretions. The absence of a cough reflex is an important risk factor for the development of pneumonia. Our patient group in our study (such as neurological diseases, genetic and cardiac diseases) has an important risk factor that does not have a cough reflex and therefore affects the development, course, and possible complications of pneumonia.[31,32] However, the frequency of pneumonia was not high in our study and patient profile. Malnutrition also increases the severity of pneumonia and mortality. The effect of malnutrition on both protein and vitamin-mineral levels is a risk factor for pneumonia.[33-35] The relationship between vitamin D and zinc (Zn) levels and pneumonia was investigated, and it was revealed that vitamin and mineral deficiencies predispose to pneumonia.[36,37] In our study, we demonstrated a negative relationship between the income level of the family and the intake of nutritional support. Again, we detected a negative relationship between education level and vitamin D levels and a negative relationship between Zn levels in patients with cardiovascular system disease. These different results may have been found in pediatric palliative care patients due to multiple and complex problems. Similarly, we found no difference between sociodemographic characteristics and viral and bacterial types of pneumonia. This may also be due to the small number of our patients. No correlation was found between MBS scores and demographic characteristics. MBS scores were also not different in terms of viral and bacterial types of pneumonia. All these suggested that the severity of dyspnea was independent of pneumonia and sociodemographic features, radiological and laboratory findings.

Table 2a.
Characteristics of patients with bacterial and viral pneumonia[§]

	Bacterial	Viral	p value
Age **[median, (IQR)]**	3.00 (6)	5.00 (7)	0.543
Number of siblings **[median, (IQR)]**	1.00 (1)	1.00 (1)	0.172
WBC **[median, (IQR)]**	12.505 (8.223)	1.0545 (8.838)	0.711
CRP **[median, (IQR)]**	0.20 (4.15)	1.21 (3.68)	0.240
Hemoglobin **[median, (IQR)]**	10.90 (2.0)	11.65 (3.2)	0.472
HTC **[median, (IQR)]**	34.15 (5)	34.50 (10)	0.588
MCV **[median, (IQR)]**	84.00 (9)	84.00 (12)	0.938
PLT **[median, (IQR)]**	294.00 (149)	366.00 (162)	0.153
Zinc **[median, (IQR)]**	66.60 (55.8)	55.85 (-)	0.641
Vitamin D **[median, (IQR)]**	25.30 (23.7)	34.65 (14.8)	0.189
Length of stay **[median, (IQR) (day)]**	14.50 (23)	18.50 (21)	0.881
Number of hospitalizations **[median, (IQR) year]**	1.00 (1)	1.00 (0)	0.166
Gender **[n (%)]** Girl Boy	 28 (80.0%) 30 (81.1%)	 7 (20.0%) 7 (18.9%)	1.000
Respiratory support **[n (%)]** No Yes (CPAP, Home-MV)[†]	 40 (78.4%) 18 (85.7%)	 11 (21.6%) 3 (14.3%)	0.744
Nutricion support **[n (%)]** Normal Supported (NG, gastrostomy)	 13 (76.5%) 45 (81.8%)	 4 (23.5%) 10 (18.2%)	0.728
Cardiovascular disease **[n (%)]** No Yes	 49 (80.3%) 9 (81.8%)	 12 (19.7%) 2 (18.2%)	1.000
Neurologic comorbidity **[n (%)]** No seizure Seizure	 16 (84.2%) 42 (79.2%)	 3 (15.8%) 11 (20.8%)	0.747

[§]Differentiation was made according to radiological evaluation, WBC; White blood cell, CRP; C-reactive protein, MCV; Mean corpuscular volume, HTC; Hematocrit, PLT; Platelet, [†]O_2; Oxygen support with a mask or nasal cannula, CPAP; Continuous positive airway pressure, Home-MV; Home-type mechanical ventilator, NG; Nasogastric tube, IQR; Ranges of quarters

Table 2b.
Characteristics of parents of patients with bacterial and viral pneumonia[§]

	Bacterial	Viral	p value
Parent age **[n (%)]** <30 30-40 >40	 17 (70.8%) 26 (83.9%) 15 (88.2%)	 7 (29.2%) 5 (16.1%) 2 (11.8%)	0.316
Parent gender **[n (%)]** Female Male	 53 (80.3%) 5 (83.3%)	 13 (19.7%) 1 (16.7%)	1.000
Parent education **[n (%)]** Primary-secondary school High school-university	 6 (85.7%) 52 (80.0%)	 1 (14.3%) 13 (20.0%)	1.000
Marital status **[n (%)]** Single Married Divorced-separated	 2 52 (78.8%) 4	 - 14 (21.2%) -	0.454
Income status* **[n (%)]** ≤3000 >3000	 29 (82.9%) 29 (78.4%)	 6 (17.1%) 8 (21.6%)	0.631
Working status **[n (%)]** House-wife Working	 46 (79.3%) 12 (85.7%)	 12 (20.7%) 2 (14.3%)	0.587
Home status **[n (%)]** Rent Own house With someone else	 36 (85.7%) 19 (73.1%) 3 (75.0%)	 6 (14.3%) 7 (26.9%) 1 (25.0%)	0.423

[§]Differentiation was made according to radiological evaluation
*It is determined according to the minimum wage in our country

Table 3.
Relationship between the radiological evaluation of pneumonia cases and MBS[§]

	MBS value		p value
	Median	IQR	
Types of pneumonia **[median, (IQR)]**			
Lobar infiltration	7.00	4	
Bronchopneumonia	6.00	5	0.613
Ground glass infiltration	7.00	3	
Interstitiel pneumonia	5.00	6	
Pathogen **[median, (IQR)]**			
Pneumococcus+bacteria **(=bacterial)**	6.50	5	0.948
Viral+atipical **(=Viral)**	6.50	5	

[§]Differentiation was made according to radiological evaluation
MBS; Modified Borg Scale, IQR; Ranges of quarters

Complete blood count and acute phase reactants do not show a specific finding in diagnosing pneumonia in children. Although infiltrates on chest radiographs support the diagnosis of pneumonia, the diagnostic value of radiological imaging in children is low in the diagnosis and differentiation of bacterial-viral pneumonia.[38,39] Segmental consolidation and lobar consolidation can be evaluated in favor of especially pneumococcal and bacterial infection, while diffuse bronchopneumonia and interstitial appearance can be evaluated in favor of viral and atypical pathogens, but its sensitivity is low.[40-42] In our study, a classification was made similar to the study of Şahin et al.[43] and MBS scores were examined accordingly. Laboratory parameters did not differ in terms of pneumonia and viral-bacterial types of pneumonia. MBS scores and laboratory parameters did not change. This result suggested that the severity of dyspnea was not related to laboratory findings in patients with pneumonia. In our study, when the radiological diagnosis of pneumonia, types, and classification of possible pathogens were examined, it was found that there was no difference in MBS scores of the cases diagnosed with pneumonia clinically. This demonstrated that the severity of dyspnea was not related to the radiological findings in pneumonia. Despite the above-average MBS scores (5.50), the severity of dyspnea in patients diagnosed with pneumonia is not correlated with radiological and laboratory findings.

Study Limitations

This study was a single-center study and may not be generalizable to other centers. In patients diagnosed with pneumonia, the sensitivity and reliability of chest radiography were low in distinguishing between bacterial and viral pneumonia. However, the use of tomography in pediatric patients was avoided due to the radiation effect. Therefore, the study was designed based on direct chest radiography. The MBS has not been validated in our patient population. To our knowledge, there is no approved scale and scoring system for dyspnea for pediatric palliative care patients. The choice of MBS for our study stems from its previous use. It is preferred for patients with a life-threatening disease or at the end of their life because of its ease of use and its representative of reality. Physical therapy and rehabilitation specialist was responsible for scoring. Many patients were not in a position to self-assess their dyspnea. Another limitation is that the study was retrospective, and analgesia and anxiolytics were not given beforehand in order to differentiate pneumonia-related dyspnea.

Table 4.
Correlations of MBS values in patients with pneumonia

		MBS value
Age	r	-0.021
	p	0.864
Number of siblings	r	0.062
	p	0.605
WBC	r	-0.058
	p	0.628
CRP	r	-0.150
	p	0.207
Hemoglobin	r	-0.073
	p	0.542
HTC	r	-0.026
	p	0.827
MCV	r	-0.117
	p	0.327
PLT	r	-0.038
	p	0.753
Zinc	r	-0.185
	p	0.545
Vitamin D	r	-0.101
	p	0.510
Length of stay (day)	r	0.005
	p	0.970
Number of hospitalizations (year)	r	-0.065
	p	0.585
Respiratory support	r_s	0.009
	p	0.941
Nutricion support	r_s	-0.115
	P	0.335
CVS disease	rs	-0.002
	p	0.988
NC (epilepsy)	r_s	0.044
	p	0.716
Parent education	r	0.082
	p	0.493
Parent income	r	0.113
	p	0.345
Parent working status	rs	-0.080
	p	0.503

r; Pearson correlation coefficient, r_s; Spearman correlation coefficient, WBC; White blood cell, CRP; C-reactive protein, MCV; Mean corpuscular volume, HTC; Hematocrit, CVS; Cardiovascular system, NC; Neurological comorbidity, PLT; Platelet, MBS; Modified Borg Scale

Conclusion

The results of this study showed that the severity of dyspnea in patients with pneumonia was not associated with pneumonia and pneumonia type. Although the MBS has use in pediatric palliative care patients, it does not show specificity for pneumonia. Causes of dyspnea

Table 5.
Parameters with significant correlation in patients with pneumonia

		Number of siblings	WBC	CRP	Hemoglobin	HTC	MCV	Zinc	Vitamin D	Respiratory support	Nutrition support	CVS disease	Number of hospitalizations (year)	Parent income
Age	r	**0.305**	-0.018	**0.379**	0.116	0.093	0.187	-0.200	**-0.514**	**-0.321**	**-0.330**	**0.246**	0.043	0.107
	p	**0.009***	0.884	**0.001***	0.331	0.438	0.116	0.512	**0.000***	**0.006***	**0.005***	**0.037***	0.721	0.371
CRP	r	0.021	0.220	1	-0.116	-0.069	0.041	-0.447	-0.268	-0.030	-0.007	0.113	**0.259**	0.122
	p	0.858	0.063		0.332	0.565	0.731	0.125	0.075	0.802	0.957	0.344	**0.028***	0.307
PLT	r	-0.133	**0.243**	0.163	-0.101	-0.034	**-0.347**	-0.127	-0.058	0.047	0.088	-0.200	0.051	-0.008
	p	0.266	**0.040***	0.170	0.398	0.775	**0.003***	0.680	0.704	0.696	0.463	0.092	0.670	0.945
Length of stay (day)	r	-0.020	0.039	0.162	-0.096	-0.052	-0.102	0.016	0.091	0.196	**0.300**	-0.018	**0.758**	**-0.235**
	p	0.868	0.747	0.173	0.421	0.666	0.395	0.959	0.552	0.099	**0.011***	0.880	**0.000***	**0.047***
Respiratory support	r_s	**-0.441**	0.156	-0.160	-0.185	-0.135	-0.013	0.488	**0.438**	1	0.213	0.067	0.184	-0.171
	p	**0.000***	0.191	0.180	0.119	0.257	0.917	0.091	**0.003***		0.073	0.575	0.121	0.152
Nutrition support	r_s	-0.018	0.147	0.040	-0.013	0.003	-0.072	0.356	**0.295**	0.213	1	-0.128	0.235	-0.344
	p	0.879	0.217	0.736	0.916	0.979	0.550	0.232	**0.049***	0.073		0.286	0.047*	0.003
CVS disease	r_s	0.009	**-0.268**	0.076	-0.039	-0.026	0.178	**-0.570**	0.019	0.067	-0.128	1	-0.055	-0.050
	p	0.941	**0.023***	0.527	0.745	0.828	0.136	**0.042***	0.900	0.575	0.286		0.645	0.674
NC (epilepsy)	r_s	0.220	-0.195	-0.004	**0.338**	**0.336**	-0.017	-	-0.015	**-0.240**	0.112	**-0.271**	-0.050	0.174
	p	0.063	0.101	0.975	**0.004***	**0.004***	0.889	-	0.920	**0.043***	0.347	**0.021***	0.679	0.143
Parent education	r	0.094	0.135	0.144	-0.003	-	-0.053	-	**-0.303**	-0.202	-0.182	0.139	0.014	**0.244**
	p	0.433	0.257	0.227	0.977	-	0.658	-	**0.043***	0.089	0.125	0.243	0.904	0.039*
Parent income	r	**0.244**	0.149	0.061	-0.093	-0.060	-0.115	-0.296	-0.134	-0.171	**-0.344**	-0.050	-0.103	1
	p	**0.039***	0.211	0.613	0.437	0.619	0.336	0.326	0.382	0.152	**0.003***	0.674	0.389	
Parent working status	r_s	0.101	0.208	0.158	-0.003	-0.024	-0.137	-0.045	-0.065	-0.006	-0.057	-0.111	0.138	**0.337**
	p	0.397	0.080	0.185	0.978	0.844	0.251	0.885	0.672	0.957	0.632	0.353	0.248	**0.004***

r; Pearson correlation coefficient, r_s; Spearman correlation coefficient, WBC; White blood cell, CRP; C-reactive protein, MCV; Mean corpuscular volume, HTC; Hematocrit, CVS; Cardiovascular system, NC; Neurological comorbidity, PLT; Platelet

other than pneumonia, which is common in pediatric palliative care patients, should be investigated, and treatment should be given for its etiology.

Author Contributions: Harputoğlu N: Concept, design, data collection or processing, analysis or interpretation, literature search, writing; Coşkun M: Concept, data collection or processing, literature search; Çubukçu D: Concept, design, analysis or interpretation; Çelik T: Design, data collection or processing, analysis or interpretation.

Conflict of Interest: There are no conflicts of interest in connection with this paper, and the material described is not under publication or consideration for publication elsewhere.

Ethical Approval: Ethics committee approval for the study was obtained from University of Health Sciences Turkey, İzmir Dr. Behçet Uz Training and Research Hospital Ethics Committee (Approval date:14/01/2021, Approval number: 20). The parents who met inclusion criteria provided verbal and written consent before participating in the study. All study procedures were conducted in accordance with the Declaration of Helsinki and local laws and regulations.

Financial Disclosure: The authors declared that this study received no financial support.

Informed Consent: No conflict of interest was declared by the authors.

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Journal of Pediatric Academy

Original Article

Year: 2023 Volume: 4 Issue: 1
Doi: 10.4274/jpea.2023.202
J Pediatr Acad 2023; 4: 33-38

Is There a Relationship Between Vitamin D Level and Iron Deficiency Anemia in Children?

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Article Information

Article Type: Original Articles
Article Group: Pediatric Rheumatology

Received: 28.11.2022
Accepted: 13.03.2023
Available Online: 31.03.2023

Cite this article as: *Özdemir Kaçer E, Kılıçaslan C. Is There a Relationship Between Vitamin D Level and Iron Deficiency Anemia in Children?. J Pediatr Acad 2023; 4: 33-38*

Abstract

Iron deficiency anemia (IDA) is the most common type of anemia in children and a major cause of morbidity and mortality. Vitamin D deficiency (VDD) is a growing public health issue that has been connected to several chronic diseases, such as osteoporosis, cancer, and metabolic syndrome. Recently, in a meta-analytic study conducted on both children and adults, it was clearly shown that there is a relationship between VDD and the risk of anemia. In this study, we wanted to review the prevalence of vitamin D insufficiency in children with IDA. We conducted a retrospective review of patient records from January 2017 to December 2019 to identify individuals aged 4 months to 18 years who had been diagnosed with IDA. Demographic data, dietary patterns, nutritional supplements, Vitamin D levels, and laboratory tests were recorded. Two hundred thirty girls and 198 boys were enrolled in the study, bringing the total number of patients to 428. The patients had a mean age of 7.24±5.1 months. The distribution of female gender according to vitamin D groups (normal, insufficient, deficient) was 85, 103, and 42, respectively; the male gender is 78, 89, and 31, respectively (p=0.745). No statistically significant difference was found between nutrition categories and vitamin D groups in different age groups (p=0.293; p=0.238; p=0.396). No statistically significant difference was found between continuous quantitative variables such as age, hemoglobin, and ferritin and vitamin D groups in different age groups (p=0.885; p=0.168; p=0.728). There was no significant association observed between the severity of anemia and VDD in children with IDA in our study. In the diagnosis of IDA, it may be useful to look at vitamin D levels by considering the time of admission. Further studies are needed for the association between vitamin D levels and IDA.

Keywords: Dietary pattern, Iron deficiency anemia, Pediatrics, Vitamin D deficiency

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Introduction

Iron deficiency anemia (IDA) is the most common type of anemia in children and a major cause of morbidity and mortality.[1] Since feeding infants only with breast milk is a risk factor for IDA, iron supplementation is necessary. Anemia can be caused by various factors, such as insufficient iron intake, chronic disease, chronic blood loss, hemolysis, malabsorption or a combination of these.[2] In a study, infants who received iron supplements had higher developmental and psychomotor scores at 13 months compared to those who did not receive iron supplements.[3]

Highlights

- Iron deficiency anemia and vitamin D deficiency are common in childhood.
- Vitamin D measurement, which is not a routine test, should be performed in IDA patients.
- Vitamin D supplementation should be started rapidly in children with vitamin D deficiency.

Vitamin D deficiency (VDD) is a growing public health issue that has been connected to several chronic diseases, such as osteoporosis, cancer, and metabolic syndrome.[4] New information on the biological functions of vitamin D has sparked interest in the clinical consequences of VDD.[5] In a study conducted in the USA, approximately 70% of children and adolescents were found to have 25-hydroxy vitamin D [25 OH)D] deficiency.[6] Several studies have been conducted on the role of vitamin D in erythropoiesis, and it has been shown that vitamin D affects bone marrow functions[5]. Additionally, studies have shown that 1, 25(OH)D levels are several hundred times higher in the bone marrow compared to plasma.[7]

Recently, in a meta-analytic study conducted on both children and adults, it was clearly shown that there is a relationship between VDD and the risk of anemia.[8] This relationship highlighted the erythropoietic function of calcitriol, given the effects of iron on metabolism and the immune system. However, VDD has also been reported in children, adolescents, and adults with IDA, but a causal relationship hypothesis could not be established.[9,10] We think that VDD may be effective in iron metabolism and IDA.

In this study, we wanted to review the prevalence of IDA in children with VDD and we wanted to review the correlation between the severity of VDD and IDA.

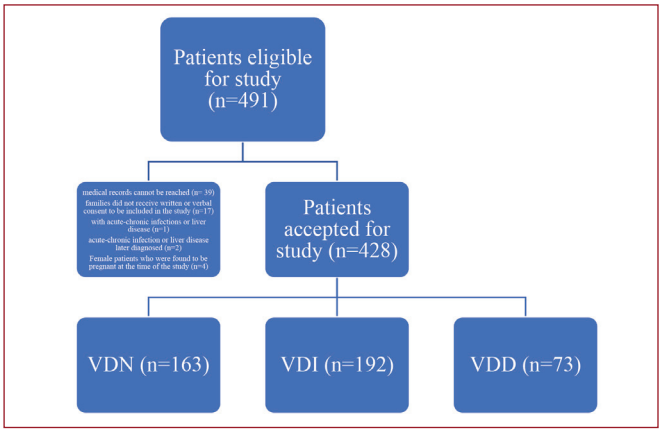
Material and Method

Research Strategy

This retrospective descriptive study was conducted in the pediatric department of a tertiary hospital in Aksaray, Turkey. Our study adhered to the guidelines set forth in the Declaration of Helsinki and was granted approval by the Aksaray University School of Medicine, Aksaray Education and Research Hospital Scientific Research Evaluation Committee, with decision number 2020/06-38. (Decision no: 2020/06-38. Date: 22/06/2020). We conducted a retrospective review of patient records from January 2017 to December 2019 to identify individuals aged 4 months to 18 years who had been diagnosed with IDA. Four hundred ninety one patients were eligible for study. Sixty three patients were excluded from study. Distribution of patients included and excluded from the study shown in Flowchart. Four hundred and twenty eight patients were identified and their data were recorded. Demographic data (age, gender, etc.), dietary patterns (breast milk, cow's milk, formula use, etc.), and nutritional supplements were collected from the database. Patients whose data were missing from the hospital records and who were contacted by telephone and whose data were completed were included in the study. Anemia treatment or dietary supplement given was recorded. Based on their age, the patients were categorized into three groups: 4 months to 6 years, 7 years to 12 years, and 13 years to 18 years. According to their dietary habits, the patients were grouped into three categories for the study. Patients aged 4 months to 6 years were divided into 3 groups breast-fed, formula-fed, and cow-goat milk and supplementary foods. The first group of patients aged 7-12 and 13-18 years is those who regularly eat meat, salmon, sardines, egg yolk, shrimp, yogurt, cereals, milk, and orange juice, the second group is those who are fed fast food and ready-made food, and the third group is meat and protein-poor diets or vegetarians.[11] The patients were divided into 3 groups according to their vitamin D levels; those with IDA and normal vitamin D (VDN), those with IDA and vitamin D insufficiency (VDI), and those with IDA and VDD. Fast food and ready-made food nutrition were defined as the consumption of ready, frozen, or packaged food outside the home at least 3 days a week for 1 or more meals and between meals.[12] A vegetarian diet was accepted as one that does not include meat (including fowl), seafood, or products containing those foods.[13] A protein-poor diet was accepted as 0.6-0.8 g/kg/day or less protein intake.[14]

Inclusion and Exclusion Criteria

- IDA criteria in children;[15]
- Hemoglobin (Hb) level <11 g/dL,
- Serum ferritin level (both men and women) <12 ng/mL,
- Mean corpuscular volüme <70 fL,
- Increased red blood cell distribution width,
- Transferrin saturation <15%.



Flowcart. Distribution of patients included and excluded from the study

VDN; Normal vitamin D, VDI; Vitamin D insufficiency, VDD; Vitamin D deficiency

Serum ferritin, which is a biomarker of iron stores in the body, is also an acute-phase reactant that can increase in response to inflammatory conditions such as infection, chronic inflammation, or liver disease. For this reason, children who were healthy and had no findings at the end of the examination were included in the study.

There is currently no consensus on how to measure and define VDD in children.[16] In our study, a serum 25(OH) D level of less than 20 ng/mL was defined as VDD; a serum 25(OH)D level of 20 to 30 ng/mL was defined as VDI.[6,17] Serum 25(OH)D levels were measured with a radioimmunoassay kit from DiaSorin (Stillwater, MN, USA).

Inclusion criteria;

- Patients who meet criteria for IDA,
- Patients whose medical records can be accessed,
- Patients whose families received verbal consent to be included in the study,
- Patients without acute-chronic infections or liver disease,
- Patients aged 4 months-18 years.

Exclusion criteria;

- Patients who do not meet the criteria for IDA,
- Patients whose medical records cannot be reached,
- Patients whose families did not receive verbal consent to be included in the study,
- Patients with acute-chronic infections or liver disease.

Criteria for exclusion during or after study;

- Patients with acute-chronic infection or liver disease later diagnosed,
- Female patients under the age of 18 who were found to be pregnant at the time of the study.

Statistical Analysis

The statistical analysis was conducted using Statistical Package for the Social Sciences version 20.0 (IBM, Armonk, NY, USA). To determine whether the variables were normally distributed, both visual methods such as histograms and probability plots, and analytical methods such as the Kolmogorov-Smirnov test, skewness, and kurtosis were used. Continuous data were reported as median (minimum-maximum) and mean ± standard deviation, while categorical variables were reported as frequencies and percentages. The chi-square or Fisher's exact test was used to compare categorical variables, while the Kruskal-Wallis and/or ANOVA tests were used to compare continuous variables for more than two independent groups.

Results

A total of 428 patients, 230 (53.7%) girls, and 198 (46.3%) boys were included in the study. The distribution of female gender according to vitamin D groups (VDN, VDI, VDD) was 85, 103, and 42, respectively; the male gender is 78, 89, and 31, respectively (p=0.745). The mean age of all patients was 7.24±5.1 months. The mean age in patients with IDA was 7.26±5.14; in patients with VDI was 7.31±4.94, and in patients with VDD was 7.31± 4 (p=0.885).

Of 428 patients, 192 (44.8%) had VDI and 73 (17%) had VDD. Of 214 children aged 4 months to 6 years, 93 (43.46) had VDI and 37 (17.29%) had VDD. Of 132 children aged 7-12 years, 65 (49.24) had VDI and 22 (16.6%) had VDD. Of 82 children aged 13-18 years, 34 (41.46%) had VDD and 14 (17.07) had VDD (p=0.779). The chi-square test was utilized to explore the associations between variables, such as gender and age groups, and vitamin D levels. Upon examining the obtained p values, no significant difference was observed between these groups concerning the variables listed in the table. **Table 1** presents the distribution of vitamin D groups based on gender and age groups.

The examination of age groups in terms of vitamin D groups according to nutrition categories was carried out with the Mantel-Haenszel chi-square test, and no difference was observed in terms of distribution between nutrition categories and vitamin D groups in different age groups (p=0.293; p=0.238; p=0.396). Therefore, there is no conditional independence between groups (p=0.367). The distribution of vitamin D groups according to their feeding patterns shown in **Table 2**.

VDI was present in 78 (50.32%) and VDD in 25 (16.13%) of 155 patients who applied during the summer season. VDI was present in 53 (40.77) and 25 (19.23) 130 patients admitted during the winter season. Of the 77 patients admitted in the spring, 34 (44.16%) had VDI and 18 (23.38%) had VDD. Of 66 patients admitted in the autumn season, 28 (42.42%) had VDI and 5 (7.58%) had VDD. The chi-square test was utilized to examine the association between vitamin D groups and seasonal admission numbers, and after analyzing the obtained p values, no significant difference was found between these groups regarding the variables presented in the table (p=0.069). Vitamin D groups and seasonal admission numbers are shown in **Table 3**.

The mean values of hemoglobin and ferritin levels were calculated according to age groups. Continuous quantitative variables such as age, hemoglobin, and ferritin were compared between vitamin D groups and no significant difference was found (p values; 0.885;

Table 1.
Comparison of the children with IDA in terms of age and gender according to the vitamin D levels

		VDN (%)	VDI (%)	VDD (%)	p value
Age group	<4 months-6 years	84 (39.25)	93 (43.46)	37 (17.29)	0.779
	7-12 years	45 (34.09)	65 (49.24)	22 (16.67)	
	13-18 years	34 (41.46)	34 (41.46)	22 (17.07)	
Gender	Female	85 (36.96)	103 (44.78)	42 (18.26)	0.745
	Male	78 (39.39)	89 (44.95)	31 (15.66)	

IDA; Iron deficiency anemia, VDN; Normal vitamin D, VDI; Vitamin D insufficiency, VDD; Vitamin D deficiency

0.168; 0.728, respectively). The comparison of vitamin D groups in terms of age, hemoglobin, and ferritin is shown in **Table 4** and **Figure a, b, c**.

Discussion

Our study is the first to compare our region's IDA and VDD. Of 428 patients diagnosed with IDA, 45% had VDI and 17% had VDD. Vitamin D was not sufficient in 62% of children diagnosed with IDA.

In our study, serum Hb and ferritin concentrations do not differ according to seasons and age groups, but when we look at the age groups, the number of patients with IDA between the ages of 4 months and 6 years was higher in our study. Although we expect to see more VDD in the lower age group due to reasons such as rapid growth, decreased vitamin D stores, increased vitamin D requirement and insufficient sun exposure, the prevalence of vitamin D in anemic children in our study does not statistically differ according to age.

The American Academy of Pediatrics recommended that 400 IU of vitamin D daily be given to all infants regardless of whether they are given formula or not since breast milk contains low vitamin D.[18] Our study, consistent with the literature, found that the prevalence of vitamin D in children with IDA did not differ according to their diet. According to the results of the study, daily vitamin D supplementation can prevent more than 60% of vitamin D deficiency.

Yoon et al.[9] demonstrated that VDD has a high prevalence in children with IDA. However, there are also studies showing no association with the prevalence of vitamin D in children with iron deficiency anemia.[19] In our study, no correlation was found regarding the prevalence of vitamin D in children with iron deficiency. Further studies are needed for the association between VDD and anemia.

Our study observed that most admissions in children with IDA and low vitamin D levels were in winter and summer. Previous studies have shown that serum 25(OH)D levels are significantly lower in spring and winter than in autumn and summer.[20] Although it was not statistically significant in our study, we think that the seasonal effect is important in VDD accompanying IDA. One of the important points that should not be ignored is that anemic children are generally sluggish and tired. This may cause children to go out less and be exposed to sunlight, which may predispose them to VDD.[21]

Although our study did not find a significant relationship between the severity of anemia and low serum 25(OH) D levels, previous research has suggested a role for vitamin D in erythropoiesis.[22] Another study found that people with VDD have a higher prevalence and risk of

Table 2.
The distribution of the children with IDA, VDI, and VDD according to their feeding patterns

Age group	Diet	IDA	VDI	VDD	p1	p2
<4 months-6 years	Breast-fed	53 (63.1)	64 (68.8)	25 (67.6)	0.293	0.367
	Fed with cow's milk or supplementary foods	20 (23.8)	16 (17.2)	11 (29.7)		
	Formula-fed	11 (13.1)	13 (14.0)	1 (2.7)		
7-12 years	*Regular nutrition	19 (42.2)	36 (55.4)	10 (45.5)	0.238	
	Fast food nutrition	13 (28.9)	22 (33.8)	8 (36.4)		
	Protein-poor or vegetarian diet	13 (28.9)	7 (10.8)	4 (18.2)		
13-18 years	*Regular nutrition	26 (76.5)	22 (64.7)	8 (57.1)	0.396	
	Fast food nutrition	4 (11.8)	6 (17.6)	5 (25.7)		
	Protein-poor or vegetarian diet	4 (11.8)	6 (17.6)	1 (7.1)		

*Meat, salmon, sardines, egg yolks, shrimp, yogurt, cereals, milk, orange juice
IDA; Iron deficiency anemia, VDI; Vitamin D insufficiency, VDD; Vitamin D deficiency

Table 3.
Vitamin D groups and seasonal admission numbers

Season	VDN		VDI		VDD		p value
Summer	52	33.55%	78	50.32%	25	16.13%	0.069
Winter	53	40.77%	52	40%	25	19.23%	
Spring	25	32.47%	34	44.16%	18	23.38%	
Autumn	33	50%	28	42.42%	5	7.58%	

VDN; Normal vitamin D, VDI; Vitamin D insufficiency, VDD; Vitamin D deficiency

Table 4.
The comparison of VDN, VDI, and VDD groups in terms of age, hemoglobin, and ferritin

	VDN		VDI		VDD		p value
Age	7.26±5.14	6 (1-19)	7.31±4,.94	7 (1-19)	7.03±5.04	6 (1-19)	0.885*
Hb	9.57±0.85	9.8 (7.8-10.9)	9.4±0.87	9.3 (7.8-10.9)	9.45±0.96	9.3 (7.8-10.9)	0.168
Ferritin	8.52±2.05	8.8 (5-11.5)	8.67±2.15	8.95 (4-11.9)	8.56±2.03	9 (5.2-11.8)	0.721

VDN; Normal vitamin D, VDI; Vitamin D insufficiency, VDD; Vitamin D deficiency, Hb; Hemoglobin
Results as descriptive statistics mean±standard deviation and median (min.-max.)
*Shows One-Way ANOVA result, all others are Kruskal-Wallis test values

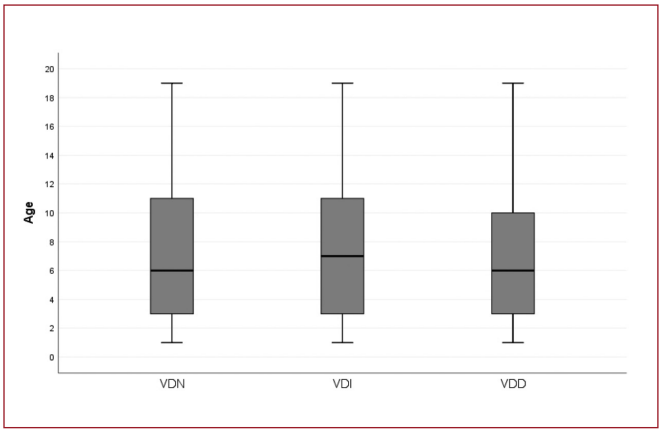


Figure a. Vitamin D groups and age

VDN; Normal vitamin D, VDI; Vitamin D insufficiency, VDD; Vitamin D deficiency

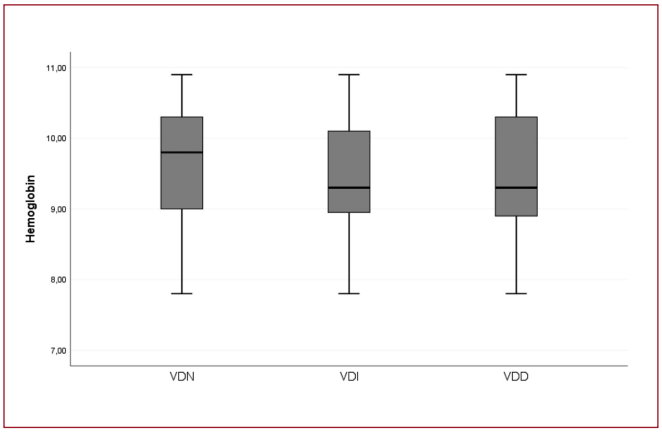


Figure b. Vitamin D groups and hemoglobin

VDN; Normal vitamin D, VDI; Vitamin D insufficiency, VDD; Vitamin D deficiency

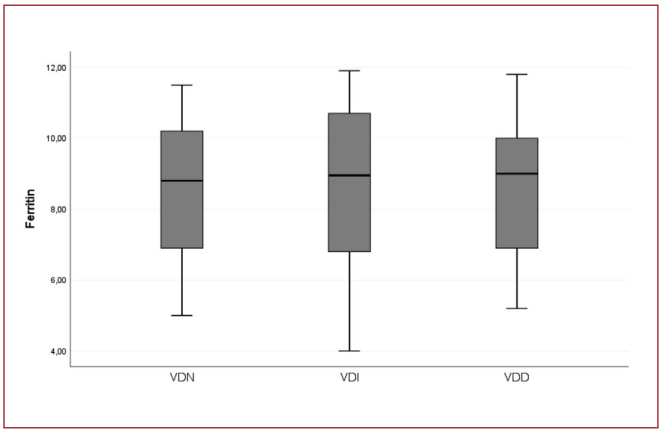


Figure c. Vitamin D groups and ferritin

VDN; Normal vitamin D, VDI; Vitamin D insufficiency, VDD; Vitamin D deficiency

anemia compared to those with VDN levels.[22] There are studies showing that VDD in children is associated with lifestyle factors such as obesity and decreased nutrition.[23] In our study, no significant correlation was found between anemia and vitamin D. More research is needed on the relationship between vitamin D and anemia in healthy children.

Kaymak Cihan and Ünver Korğalı[24] demonsrated that the longer exclusively breastfeeding is independent risk factor for IDA in children. Li et al.[25] found that infant formula intake is were protective factors for VDD and VDI. The results of our study did not demonstrate a significant relationship between feeding patterns and vitamin D levels. This may be due to regional differences and sufficient homogeneity between patient groups.

Study Limitations

Our study had some limitations. The study population was limited as the patients consisted of children with a diagnosis of IDA and no other complaints. Additionally, we did not examine a control group of healthy children. Therefore, our results regarding the prevalence of vitamin D and IDA cannot be generalized to other populations.

Conclusion

In conclusion, no correlation was found between the severity of anemia and VDD in children with IDA in our study. In the diagnosis of IDA, it may be useful to look at vitamin D levels by considering the time of admission. Further studies are needed for the association between vitamin D levels and IDA.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version. Özdemir Kaçer E: Designed study, collected and analyzed data, wrote and revised article, Kılıçaslan C: Analyzed and collected data, wrote article.

Conflict of Interest: There are no conflicts of interest in connection with this paper, and the material described is not under publication or consideration for publication elsewhere.

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients. Verbal consent from was obtained from patients and their parents.

Ethics Committee Approval: The study was conducted in compliance with the Declaration of Helsinki and approved by Aksaray University School of Medicine, Aksaray Education and Research Hospital Scientific Research Evaluation Committee with (Decision no: 2020/06-38. Date: 22/06/2020).

Financial Disclosure: The authors declared that this study received no financial support.

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Journal of Pediatric Academy

Case Report

Year: 2023 Volume: 4 Issue: 1
Doi: 10.4274/jpea.2023.193
J Pediatr Acad 2023; 4: 39-41

Exfoliative Cheilitis in Childhood: A Successful Treatment with Tacrolimus

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Article Information

Article Type: Case Report
Article Group: Pediatric Rheumatology

Received: 15.08.2022
Accepted: 16.10.2022
Available Online: 31.03.2023

Cite this article as: *Ulusoy E, Abacı A. Exfoliative Cheilitis in Childhood: A Successful Treatment with Tacrolimus. J Pediatr Acad 2023; 4: 39-41*

Abstract

Exfoliative cheilitis is a hardly diagnosed disease by pediatricians. We have presented this report to draw the attention of clinicians because the child is the youngest patient with complete relief from using tacrolimus ointment in the literature. We present the three-year-old child with scaled, crusted, and sensitive upper and lower lips. He was admitted to different centers from the beginning of the complaints without any relief despite different treatments. The clinicians may encounter exfoliative cheilitis in different age groups. There are some approaches to management and therapy of the disease. But consensus has not yet occurred on definitive treatment, especially in childhood.

Keywords: Exfoliative cheilitis, children, tacrolimus

Introduction

Cheilitis is an acute or chronic inflammation that affects the vermillion of the lips. It is also a cosmetic problem. There are different types of this process: plasma cell cheilitis, cheilitis glandularis, actinic cheilitis, contact cheilitis, angular cheilitis, cheilitis granulomatosa, exfoliative cheilitis, and factitious cheilitis.[1]

Exfoliative cheilitis is an uncommon chronic inflammatory type of lip disease. The etiology of the disorder is still unknown. It presents with desquamation of a thick keratin scale, sensitivity, burning sensation, and sometimes fissuring of the lips.[2]

In the literature, the reported cases are in adolescent or adult age groups.[3] Because of the rare condition of the disease, the clinicians may be overlooked. Here we report the youngest patient with exfoliative cheilitis to our knowledge in the literature. The objective of the present paper is to pay attention to the disease in the childhood age group.

Case Report

The three-year-old child presented to our child health department with the chief complaints of scaled, crusted, and sensitive upper and lower lips. The lesion first appeared six months ago and gradually increased. Burning and itchy sensation, and fissuring of the lips were added to the complaint but the pain was absent. General physical examination was normal except for a painless, crusted area

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on the upper and lower lips (**Figure 1**). The crust was loosely adherent and detached easily in most places. On the lesion, there weren't any findings suggestive infectious process. Palpable head or neck lymph nodes were absent. Also, no other oral or skin lesions were noted. Lip licking and biting associated with underlying stress and anxiety because of sibling rivalry were learned. Although daily activities like eating or speaking were sometimes difficult because of the sensitivity of the lips, did not cause serious problems such as lack of weight loss. When determining personal and family medical history any specific conditions were not found.

He admitted different centers from the beginning of the complaints. Previous treatment had included the local application of corticosteroids, antibiotics, antifungal agents, and sunscreens, also topical and systemic anti-allergic agents without complete relief. But one course of antifungal agent treatment caused only partial response.

Complete blood count, sedimentation rate, and routine serum chemistries that were investigated in previous centers were all within normal limits. Immunologic evaluation and histopathological examination weren't obtained. The exfoliative cheilitis was diagnosed with the clinical findings.

A course of topical calcineurin inhibitors (tacrolimus) ointment was prescribed with a complete response after 10 days (**Figure 2**). Also, he was advised not to do factitious behavior like biting or licking the lips. Written informed consent form was obtained from the patients.

Reported cases of exfoliative cheilitis showed that females were affected more than males.[1] But Reichart et al.[4] reported that the presence of exfoliative cheilitis was more common in male Acquired Immune Deficiency Syndrome patients. In terms of age, most of the patients were adolescents or older not in the little age group.[2] In the literature, the present patient is the youngest one to our knowledge.

The major symptoms are scaling and then being yellowish-white crust, frequently painless, which may affect just one or both lips, usually the lower. When these scales are removed, usually a normal appearing lip is revealed beneath, although there may be associated erythema and edema.[5] There are different additional complaints, such as; burning or itchy sensation, pain, ulceration, bleeding, and superficial fissure of the lips.[6] Candida infection can be added to patients with predisposition like immunocompromised situations.[7] If a secondary fungal infection is added to the lesion, a partial response can be seen by antifungal treatment like our patient.

The etiology of exfoliative cheilitis is still unknown although several factors are being considered that triggered the onset. Self-damaging behavior, sometimes done unconsciously may be seen in some of the patients.[8] These habits may be a sign of stress, anxiety, and depression situations. Depression, anxiety, and personality disorders have been reported commonly in association with factitious exfoliative cheilitis.[3,6,8] These activities also may be seen at factitious cheilitis, which is a different, self-inflicted entity. But most patients have factitious cheilitis and deny these habits. Our patient licks and bites lips starting with stressful period because of sibling rivalry. We think that the situation may be the factitious type of exfoliative cheilitis like the previous report.[2] Allergy is considered a possible cause of exfoliative cheilitis. Pigatto et al.[9] reported an exfoliative cheilitis case because of a dental implant. When viewed from this aspect, our patient has no allergic history of food or anything else.

The diagnosis of exfoliative cheilitis is based on the history and clinical findings. Laboratory tests and pathological examinations aren't obtained for the diagnostic workup. Histopathological findings are usually nonspecific.[8] If it was carried out, parakeratosis or hyperkeratosis, benign epithelial hyperplasia, acute or chronic inflammation, and fibrosis can be seen.[3] A swab culture can be taken if a suspected infection exists. Also, patch testing can be performed if allergic etiology is considered. Nevertheless, the diagnosis of exfoliative cheilitis is still based on the history and the clinical findings without any laboratory or histopathological examination.

Spontaneous improvement has been reported.[5] But it often has recurrent episodes.[2,6,8] Due to a lack of consensus on treatment, the clinicians may prefer different agents, such as; corticosteroids, keratolytic agents, sunscreen antibiotics, antifungals, tacrolimus ointment, or combination treatment.[3,5] In the case reported, topical Calendula officinal is ointment known as common marigold or pot marigold was used for

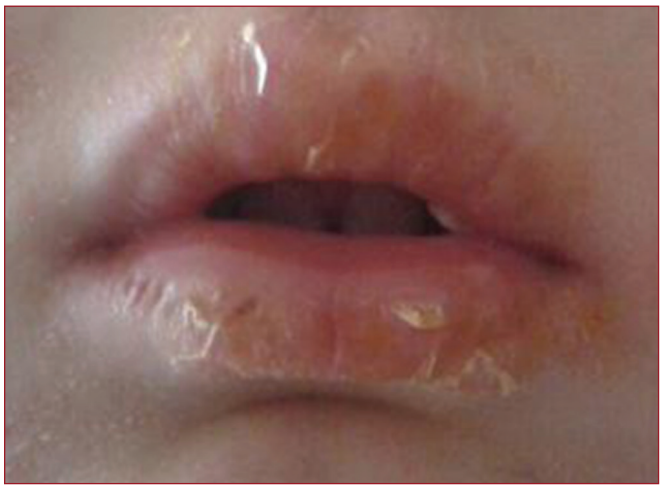

Figure 1. Scaling and crusting lips

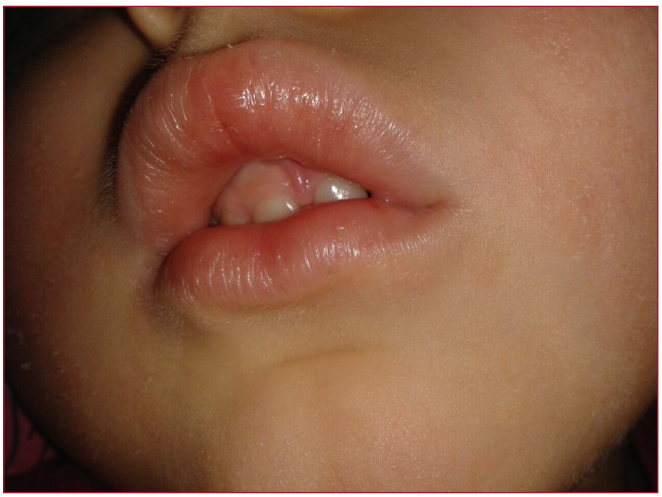

Figure 2. Treatment after tacrolimus

treatment, with complete relief.[10] Medication with antidepressants was helpful to partial response for patients with underlying depression.[2,3,6] Almazrooa et al.[3] showed all patients had complete relief and used calcineurin inhibitors, the most frequently used agent in that report. Tacrolimus is a drug isolated from streptomyces tsukubaensis, and has an effect as calcineurin inhibitors. It binds to specific receptors on T-cells to increase intracellular calcium and create an effect on several genes to change cytokines.[11] Oral tacrolimus has been used for different diseases such as preventing organ rejection in kidney and liver transplant patients.[12] As an ointment, tacrolimus is used to treatment of lupus erythematosus, vitiligo, and exfoliative dermatitis.[13-15] It suppresses inflammation like glucocorticoid agents with much fewer side effects without disturbing the collagen synthesis. A burning or itching sensation is the most common side effect, especially with application on a large surface.[16] Our patient used different agents for this complaint; corticosteroids, antibiotics, antifungal agents, sunscreens, also topical and systemic antiallergic agents. But the symptom persisted. In 10 days, a complete response was seen with topical tacrolimus treatment.

Conclusion

Exfoliative cheilitis is an unusual condition in childhood, which clinicians should be aware that is a clinical diagnosis without necessity further investigation, and tacrolimus ointment is an effective and safe drug for treatment resistance exfoliative cheilitis cases.

Author Contributions: Ulusoy E: Surgical and Medical Practices, Design, Data Collection or Processing, Analysis or Interpretation, Literature Search, Writing; Abacı A: Surgical and Medical Practices, Design, Literature Search.

Conflict of Interest: The authors have no conflict of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Informed Consent: Written informed consent was obtained from the parents of the patient.

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Journal of Pediatric Academy

Image Corner

Year: 2023 Volume: 4 Issue: 1
Doi: 10.4274/jpea.2023.201
J Pediatr Acad 2023; 4: 42-43

A Case of Pediatric Urticaria Pigmentosa

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Article Information

Article Type: Image Corner
Article Group: Pediatric Rheumatology

Received: 08.11.2022
Accepted: 21.11.2022
Available Online: 31.03.2023

Cite this article as: *Aydoğdu Ş, Aydoğdu İH. A Case of Pediatric Urticaria Pigmentosa. J Pediatr Acad 2023; 4: 42-43*

Case

A three-month-old boy was admitted to the dermatology clinic with the complaint of red-brown spots that started to appear on his body two months ago. In his dermatological examination, brown, some slightly erythematous macules were detected on the scalp, trunk, and extremities (**Figure 1a, b**). Darier's sign was positive (**Figure 1c**). In the histopathological examination of the biopsy, mild acanthosis and an increase in the basal layer melanin pigment content were observed in the epidermis, and diffuse mast cell infiltration was accompanied by eosinophils in the papillary dermis. In the immunophenotypic examination of mast cells, positive with tryptase and cluster of differentiation were detected. Blood tryptase level, hemogram, and liver function tests (LFT) were normal. Hepatosplenomegaly and lymphadenopathy were not observed. The patient was diagnosed with urticaria pigmentosa (UP).

Mastocytosis (M) describes a group of rare diseases seen in the excessive proliferation of mast cells in the skin and/or systemic organs (bone marrow, liver, spleen, lymph nodes). It is divided into two main groups systemic and cutaneous. There are three types of cutaneous M: UP (maculopapular cutaneous M), diffuse cutaneous M, and solitary mastocytoma.[1] UP is a common subtype that is seen mostly in children without systemic organ involvement. It presents numerous brownish macules and papules. Bullae can be seen over the lesions. It is commonly located on the trunk, neck, scalp, and distal extremities. These lesions usually occur within the first 6 months or may appear until adulthood. After rubbing the surface of lesions with a blunt object, an itchy urticarial plaque is observed, which is called the Darier's sign.[1,2]

Diagnosis is made by histopathological examination of typical skin lesions. Intense mast cell infiltration in the dermis and increased melanin in the basal layer are the most important findings.[2] Serum tryptase level, hemogram, and LFT should be normal, lymphadenomegaly and hepatosplenomegaly should not be detected for diagnosis of cutaneous M.[1] Systemic involvement is observed in very few children. It is recommended to repeat them every 10-12 months. Bone marrow biopsy is not routinely recommended in pediatric patients.[2]

Releasing of mast cell mediators causes pruritus, urticaria, flushing, abdominal pain, bone pain, diarrhea, and cardiovascular symptoms. Rarely, anaphylaxis and death have been reported. Exercise, exposure to hot and cold, emotional stress, local trauma to lesions, consumption of alcohol, spicy food, and some drugs (narcotics, salicylates, nonsteroidal anti-inflammatory drugs, vancomycin, polymyxin B, contrast agents, etc.) may trigger systemic symptoms of M.[1,2]

The differential diagnosis includes urticaria, nodular scabies, xanthogranuloma, pseudolymphoma, and spitz nevus.[1-3] There is no curative treatment for UP. Skin lesions usually regress spontaneously before puberty. Eliminate triggering factors and symptomatic treatments are recommended.

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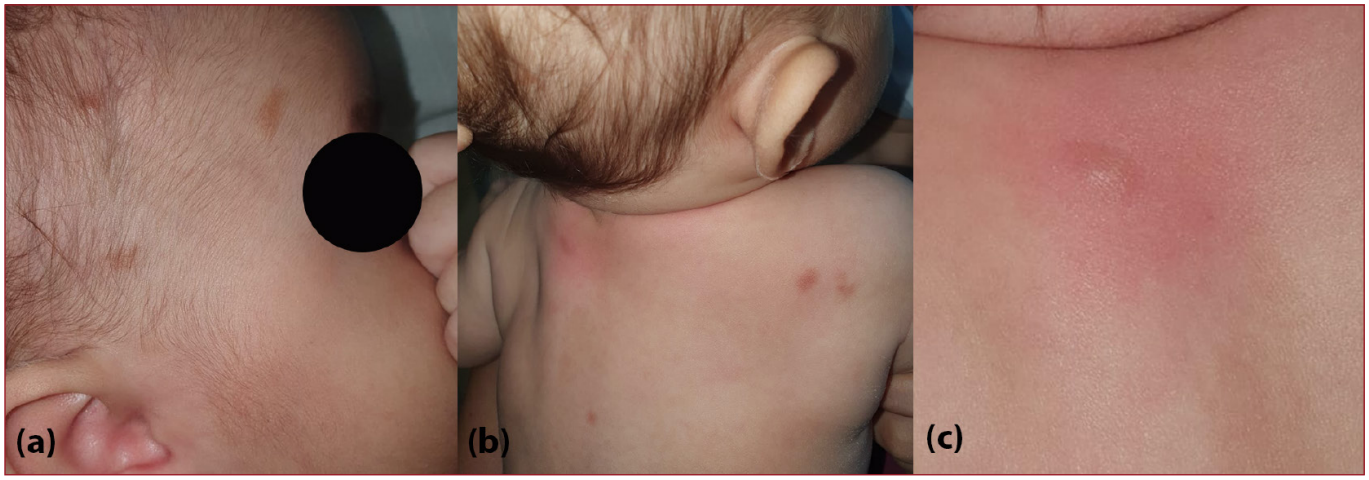

Figure 1. (a) Brown macules and papules located on the head, (b) Erythematous brown macules located on the back, (c) Darier's sign positive lesion on the back

Antihistamines, oral cromolyn sodium, steroids, and topical calcineurin inhibitors are usually used.[1]

Pediatricians see this type of rash frequently. Patients are referred to dermatology outpatient clinics in the late period or with false prediagnosis. Including M in the differential diagnosis of brown maculopapular lesions is vital for patients with this diagnosis.

Author Contributions: All of the authors declare that they have all participated in the design, exevution, and analysis of the paper, and that they have approved the final version.

Conflict of Interest: The authors have no conflict of interest to declare.

Financial Disclosure: The authors declare that this study has received no financial support.

Informed Consent: Written informed consent was ontained from the parents of the patients.

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