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PESQUISA ORIGINAL

Association of sleep disorders and clinical characteristics of children with cystic fibrosis

Associação dos distúrbios de sono e características clínicas de crianças com fibrose cística

Asociación entre los trastornos del sueño y las características clínicas de los niños con fibrosis quística

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ABSTRACT | This study aims to verify the relationship of sleep disorders (SD) with clinical features in children with cystic fibrosis. This analytical cross-sectional study was carried out in individuals with cystic fibrosis, who were divided according to their age: from two to 43 months in the infants' group (IG) and from five to 14 years in the schoolchildren's group (SG). Information on genotype, disease severity, and presence of pathogens were collected from medical records. To evaluate SD, the brief infant sleep questionnaire was applied in the IG and the sleep disturbance scale for children in the SG. Nutritional status categorized the percentiles based on the body mass index. In the SG, spirometry and pulse oscillometry were conducted. The chi-squared test was used to analyze the association between variables, and Spearman's coefficient was applied for quantitative variables ($p<0.05$). In total, 33 individuals participated in this study, with a mean age of 1.49±1.15 years in the IG and of 11.38±2.88 years in the SG. In the IG, 72.2% were eutrophic and 22.2% were prone to SD. In the SG, low weight occurred in 80% of its members and in 73.3% in the SD (a mean of 42.27±7.75 in the sleep disturbance scale for children). An association occurred between SD and nutritional status in the total sample, with SD predominating in individuals with low weight ($p=0.013$). this study found a trend toward SD in this population, especially in underweight children.

Keywords | Pediatrics; Sleep Disorders; Cystic Fibrosis.

RESUMO | O objetivo deste estudo é verificar a relação dos distúrbios do sono (DS) com características clínicas de crianças com fibrose cística (FC). Trata-se de um estudo analítico transversal em indivíduos com FC, divididos conforme a idade: 2 a 43 meses no grupo de bebês (GB); 5 a 14 anos no grupo de escolares (GE). Genótipo, gravidade da doença (ESD) e presença de patógenos foram coletados em prontuário médico. Para avaliação dos DS, aplicou-se *Brief Infant Sleep Questionnaire* (BISQ) no GB, e *Sleep Disturbance Scale for Children* (SDSC) no GE. Para o estado nutricional (EN), considerou-se a categorização dos percentis com base no índice de massa corpórea (IMC). No GE, conduziu-se a espirometria e oscilometria de impulso (IOS). Foi utilizado o teste qui-quadrado para análise da associação entre as variáveis, e aplicou-se coeficiente de *Spearman* para variáveis quantitativas ($p<0,05$). Participaram 33 indivíduos, com média de idade de 1,49±1,15 anos no GB, e 11,38±2,88 anos no GE. No GB, 72,2% eram eutróficos e 22,2% apresentaram propensão

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para DS. No GE, verificou-se baixo peso em 80% e DS em 73,3% (média do SDSC de 42,27±7,75). Houve associação entre DS e EN na amostra total, predominando DS nos indivíduos com baixo peso (p=0,013). Conclui-se que há uma tendência aos DS nessa população, principalmente em crianças com baixo peso.
Descritores | Pediatria; Transtornos do Sono-Vigília; Fibrose Cística.

RESUMEN | El objetivo de este estudio es identificar la relación entre los trastornos del sueño (TS) y las características clínicas de los niños con fibrosis quística (FQ). Se trata de un estudio analítico transversal de individuos con FQ, que se dividieron según la edad: de 2 a 43 meses en el grupo de bebés (GB); y de 5 a 14 años en el grupo de escolares (GE). El genotipo, la gravedad de la enfermedad (ESD) y la presencia de patógenos se recogieron de los historiales médicos. Para evaluar los TS, se aplicó el *Brief Infant Sleep Questionnaire* (BISQ) en el GB, y la Escala de Trastornos del Sueño para Niños (SDSC) en el EG. Para el estado nutricional (EN), se consideró la categorización de percentiles en función del índice de masa corporal (IMC). La espirometría y la oscilometría de impulso (IOS) se realizaron en el GE. Se utilizó la prueba de chi-cuadrado para analizar la asociación entre las variables, y se aplicó el coeficiente de Spearman para las variables cuantitativas (p<0,05). Participaron 33 individuos, con una edad media de 1,49±1,15 años en el GB, y 11,38±2,88 años en el GE. En el GB, el 72,2% eran eutróficos, y el 22,2% tenían una propensión a TS. En el GE, hubo bajo peso en el 80% de ellos y TS en el 73,3% (SDSC promedio de 42,27±7,75). Hubo asociación entre TS y EN en la muestra total, con predominio de TS en individuos con bajo peso (p=0,013). Se concluye que existe una tendencia a TS en esta población, especialmente en niños con bajo peso.
Palabras clave | Pediatría; Trastornos del Sueño-Vigilia; Trastornos del Sueño-Vigilia.

INTRODUCTION

Cystic fibrosis (CF) is a multisystemic health condition. However, pulmonary impairment is largely responsible for the deaths in this population, who show higher incidences of respiratory failure, pulmonary hypertension, and increased lung markings[1,2]. Individuals with airflow limitation, as in CF, are prone to show hypoxemia, hypoventilation, and hypercapnia during the rapid eye movement sleep stage[3]. This can result in sleep disorders (SD), which, according to their definition, affect individual's sleep-wake cycle, causing difficulties falling asleep and/or maintaining sleep[4,5]. Moreover, SD have been related to different manifestations in the life of persons with CF, such as difficulty falling asleep, coughing or snoring[4], reduced daytime activities, impaired immune response, and systemic (metabolic, endocrine, and cardiovascular) changes[5].

Since SD occurs in individuals who have received a diagnosis of CF, emphasizing the need to address this disorder in referral centers is of paramount importance[6] as these changes in sleep quality may be associated with poorer disease control, greater local inflammation, increased frequency of respiratory exacerbations, reduced lung function, and impaired gas exchange, which contribute to worsening quality of life[7].

Despite the recognized relevance of this approach, few studies have investigated sleep quality in CF and the repercussion of poor sleep on clinical health aspects. Thus, this study aimed to find the association of SD with clinical characteristics (pulmonary function, respiratory mechanics, nutritional status, presence of pathogens, disease severity, and genotype) in individuals with CF.

METHODOLOGY

This cross-sectional analytical study was carried out in clinically stable individuals with CF who were aged from two months to 14 years and who underwent follow-up at the CF outpatient clinic of the Joana de Gusmão Children's Hospital. Clinical stability was determined by two scores: the cystic fibrosis clinical score and cystic fibrosis foundation score. Scores >25 points or an increase >15 points in relation to the last cystic fibrosis clinical score or the presence of ≥four symptoms in the cystic fibrosis foundation score characterized disease exacerbation[8,9], in which case the patient was excluded from this research. Parents and individuals with CF signed terms in which they agreed to participate in this study (when applicable).

The included individuals were subdivided into two groups: the infants' group (IG) — the participants of which were aged from two to 43 months — and

the schoolchildren's group (SG) — for those aged from five to 14 years. Questionnaires to assess sleep quality were applied in both groups. In the IG, the guardians were asked to answer the brief infant sleep questionnaire, an instrument that assesses infant sleep and encompasses the pattern of daytime sleep and nocturnal behavior based on the sleep patterns of the week prior to assessment. The questionnaire consists of 11 questions, and the criteria to determine a worse sleep quality are (1) the child wakes up >three times a night, (2) the period of nocturnal wakefulness equals >one hour, and (3) the sleep time totals <nine hours. Children who had changes in at least one of the three listed items were classified as prone to SD[10]. For the SG, the sleep disturbance scale for children (SDSC) questionnaire was used, which is composed of 26 questions related to sleep behavior ranging from 26 to 130 points, in which scores greater than 39 characterize the propensity to SD[11].

The IG anthropometric data were collected from patients' electronic medical records as recorded by nutritional monitoring on the day of collection. In the SG, height was evaluated with a portable stadiometer (Sanny®) and body mass with a digital scale (Ultra Slim W903, Wiso®). Body mass index (BMI) was calculated to determine the categories of nutritional status according the Telessaúde Brasil Program, and was the basis for classification by percentiles: underweight <three, eutrophic ≥three and <85, overweight ≥85 and <97, and obesity ≥97[12].

In the SG, respiratory mechanics and lung function were also evaluated with the Master Screen IOS pneumatograph (Erich Jaeger, Germany®). An impulse oscillometry system was started so that the forced maneuvers of spirometry would fail to interfere with the result since IOS is conducted in tidal volume and, therefore, has been widely used in pediatrics. The standards of Beydon et al.[13] were respected. Overall, three to five measurements were performed with a minimum recording time of 20 seconds, and the maneuver with the best values of the parameters considered was considered valid: central 20-Hz airway resistance, 5-Hztotal airway resistance, resonance frequency, 5-Hz reactance – which evaluates elastic properties – and 5-Hz impedance[14,15]. The predicted values were considered according to the Brazilian equation[15]. Spirometry followed the acceptability and reproducibility criteria standardized by the American Thoracic Society[16]. The spirometric parameters analyzed were: forced vital capacity (FVC); forced expiratory volume in one second (FEV_1); FEV_1/FVC ratio; forced expiratory flow at 25%-75% of FVC (FEF_{25-75}%); and peak expiratory flow, following the predicted values in Pereira et al[17].

Electronic medical records were searched to collect data regarding the presence of pathogens, genotype, and severity of the disease. Records of the presence of pathogens considered the pathogen identified in three subsequent cultures of the last quarter[18]. As for the genotype, individuals were characterized and divided into three groups: ΔF508 heterozygous, ΔF508 homozygous, and a group with the other mutations[19]. Disease severity was classified by the medical team according to the Shwachman-Doershuk score, namely: severe if <40, moderate if 40-55, mild if 56-70, good if 71-85, and excellent if 86-100 points[19].

Statistical analysis was processed on IBM SPSS® 20.0. The Shapiro-Wilk test was applied to analyze data distribution. In the IG, variables were categorized, and the chi-squared test was applied to verify the association of the brief infant sleep questionnaire with the variables genotype, category of nutritional status, disease severity, and presence of pathogens. In the SG, Spearman's correlation coefficient was applied to analyze the relation between the SDSC score, oscillometric and spirometric parameters, nutritional status, and disease severity. The total sample was categorized according to propensity to SD, genotype, categories of nutritional status, disease severity, and presence of pathogens. Then, the chi-squared test was conducted to verify the association of these variables with SD. A significance level of 5% was considered for all tests.

RESULTS

this study included 33 individuals, 18 in the IG and 15 in the SG. In the IG, 55.6% of the sample were boys, with a mean age of 1.49±1.15 years, whereas the SG consisted of 60% of boys with a mean age of 11.38±2.88 years. As for the sleep questionnaires, four children showed propensity to SD in the IG, all of whom showed only one of the three criteria determined to evaluate the results. In the SG, 11 children had a score ≥39, classified as SD-prone, with a mean SDSC score of 42.27±7.75. Table 1 shows sample characterization data, clinical characteristics, and sleep questionnaires.

Table 1. Sample characterization, clinical characteristics, and sleep questionnaires (HIJG, 2020)

Parameter	IG (n=18)		SG (n=15)	
	Mean± SD and %	Median (min-max)	Mean± SD and %	Median (min-max)
Age (years)	1.49±1.15	0.87 (0.17-3.58)	11.38±2.88	11.83 (6.83-14.91)
BMI (Kg/m^2)	16.16±1.36	16.25(14.30-18.88)	16.69±1.95	16.33 (13.14-20.45)
Nutritional status				
Underweight	0%	NA	80.0%	NA
Eutrophic	72.2%	NA	20.0%	NA
Overweight	27.8%	NA	0%	NA
Genetic mutation				
ΔF508 homozygous	50.0%	NA	20.0%	NA
ΔF508 heterozygous	22.2%	NA	60.0%	NA
Others	27.8%	NA	20.0%	NA
Colonization				
Yes	11.1%	NA	66.7%	NA
No	88.9%	NA	33.3%	NA
ESD Classification				
Mild	5.6%	NA	20.0%	NA
Good	5.6%	NA	33.3%	NA
Excellent	88.8%	NA	47.7%	NA
SD				
Absent	77.8%	NA	26.7%	NA
Present	22.2%	NA	73.3%	NA
SDSC(points)	NA	NA	42.27±7.75	42.00 (29-56)
Spirometry				
FEV_1 (%)	NA	NA	37.48±10.53	36.28 (30.03-43.94)
FVC (%)	NA	NA	36.86±11.15	33.94 (27.68-45.43)
FEV_1/FVC (% predicted)	NA	NA	0.93±0.9	0.9 (0.9-1.03)
FEF_{25-75} (%)	NA	NA	47.35±24.14	47.35 (28.06-51.46)
PEF (%)	NA	NA	33.15±10.45	33.15 (15.98-37.24)
IOS				
Z5 (%)	NA	NA	187.33±86.51	159.82 (97.01-421.57)
R5 (%)	NA	NA	99.70±24.66	99.15 (68.43-153.54)
R20 (%)	NA	NA	87.05±14.11	88.09 (63.41-113.06)
X5 (%)	NA	NA	227.45±118.04	195.27 (104.85-518.85)
Fres (%)	NA	NA	111.74±30.55	106.53 (71.27-177.23)

Caption: IG: infants' group; SG: schoolchildren's group; SQ: sleep quality; NA: not applicable; BMI: body mass index; ESD: Shwachman-Doershuk score; SDSC: sleep disturbance scale for children; FEV_1: forced expiratory volume in one second; FVC: forced vital capacity; FEV1/FVC: ratio between FEV_1 and FVC; FEF_{25-75}: forced expiratory flow at 25-75% of FVC; PEF: peak expiratory flow; IOS: impulse oscillometry; Z5: respiratory impedance at 5Hz; R5: total airway resistance; R20: central respiratory resistance; X5: reactance at 5Hz; Fres: resonance frequency. Data shown as percentages (%), mean±SD, and median (with minimum-maximum values).

The IG showed no association with the investigated variables (genotype, nutritional status, disease severity, and presence of pathogens, p>0.05), whereas the SG showed no correlation between SDSC scores and the analyzed data (spirometric and oscillometric parameters, nutritional status, and disease severity, p>0.05). The total sample showed an association (p=0.013) between SD and nutritional status according to the BMI percentiles, with a higher incidence of SD in individuals with low weight (80%).

Table 2. Correlation between sleep questionnaires and the variables analyzed in the IG, SG, and the total sample

Infants' group (IB)				
	Genotype	**Nutritional status**	**Disease severity**	**Presence of pathogens**
BISQ Chi-square test value	5.622	0.005	0.487	0.940
p-value	0.081	0.946	0.485	0.332

Schoolchildren's Group (SG)											
	Spirometric parameters (%)				**Oscillometric parameters (%)**					**NS**	**ESD**
SDSC Correlation coefficient	FEV_1	FVC	FEF_{25-75}	PFE	Z5	R5	R20	X5	Fres		
	0.094	0.094	0.220	0.220	−.178	−.059	0.503	−.230	.082	0.421	0.324
p-value	0.738	0.738	0.430	0.430	0.494	0.822	0.093	0.374	0.754	0.552	0.337

Total sample (IG + SG)				
	Genotype	**Nutritional status**	**Disease severity**	**Presence of pathogens**
SD Chi-square test	2.877	1.743	0.429	2.072
p-value	0.237	0.013*	0.512	0.150

Caption: BISQ: brief infant sleep questionnaire. NS: nutritional status; ESD: Shwachman-Doershuk Score for disease severity assessment. SD: sleep disorders. SG: schoolchildren's group; SDSC: sleep disturbance scale for children. FEV_1 forced expiratory volume in one second; FVC: forced vital capacity. FEF_{25-75}: forced expiratory flow at 25%-75% of FVC; PEF: peak expiratory flow; Z5: airway impedance at Hz; R5: central airway resistance at 5Hz; R20: peripheral airway resistance at 20Hz; X5: airway reactance at 5 Hz; Fres: resonance frequency.

SD occurred in almost half of individuals with CF, especially in children with low weight, in relation to nutritional status. The comparison between IG and SG showed no association between SD and the investigated variables (genotype, nutritional status, disease severity, and presence of pathogens).

DISCUSSION

This study analyzed the relationship between SD and the clinical characteristics of individuals with CF and showed an association between these disorders and the nutritional status of this population, especially in those with low weight. This is relevant because nutritional deficiency is an important factor to be considered for the prognosis of this population since low weight is associated with disease severity and mortality rate[20].

It is noteworthy that low weight only occurred in the SG individuals (80% of the sample) and, in this same group, the mean FEV_1% totaled 75.83%. Likewise, an epidemiological study in adolescents and young adults with CF[21] aged from 14 to 22 years observed a greater rate of decline in FEV_1 and BMI in older individuals when comparing the two groups. This finding may justify the difference between the nutritional status of the older individuals in this study given the low weight in most children in the SG (72.2%) but in no child in the IG. Evidence exists for the significant association between low weight and worse lung function[22] and

the impairment of both with disease evolution[18,20]. Furthermore, malnutrition remains a common problem in CF patients, especially those with poor lung function[23].

In addition to nutritional parameters, the relation between SD and the respiratory system is frequently investigated in individuals with CF since the impairment of this system configures the major cause of death in this population. A study with 31 children and adolescents found SD, including obstructive sleep apnea and nocturnal hypoxemia. Of these, those who manifested nocturnal hypoxemia had reduced lung function, clinical worsening in the evaluated scores, and higher morbidity related to longer hospitalization and antibiotic use[24]. Another study also evaluated the presence of obstructive sleep apnea in children and adolescents with CF and found the high prevalence of dysfunction regardless of age and lung function impairment, reinforcing the importance of investigating SD in this population before the compromise of lung function[25]. Corroborating the above, changes in spirometry were closely related to sleep disturbances, as well as the presence of nocturnal cough, chronic pain, gastrointestinal symptoms, and changes in the hypothalamus, factors that may become potential causes of SD in CF[3].

This research conducted spirometry and impulse oscillometry as impulse oscillometry is also considered important in respiratory assessment to detect airflow obstruction in children with CF, as well as its topography. It is worth noting that, as it requires no forced maneuvers, impulse oscillometry facilitates its carrying out by younger children, which enables the investigation of this age group[26,27]. In CF, its use is recent and its main objective is to detect changes in stable patients, find early pulmonary impairment and offering an alternative to characterize the degree of this impairment in the early stages of the disease[27].

The findings of this investigation offer the identification of a worse sleep quality in the pediatric population with CF as a clinical contribution, which may draw the attention of multidisciplinary teams regarding the early management of this condition. Studies that aimed to improve the understanding of the disease in different scopes have contributed to better direct multidisciplinary follow-up[23-25], which should include sleep in its care. Moreover, the consensus suggests intervening in what can become a vicious cycle since sleep is essential to maintain the nutritional condition in this population[3], and both sleep and nutritional status are essential factors to reduce respiratory complications[22].

This pioneer study investigated possible SD in CF, relating them to pulmonary impairment and other clinical features of the disease. However, it applied specific and subjective questionnaires to evaluate SD rather than polysomnography, an instrument recognized as the gold standard for objective sleep evaluations, which can be considered a limitation. Moreover, the fact that the guardians of individuals with CF answered the questionnaires may configure a risk of bias. Moreover, this cross-sectional study has other limitations, including no information regarding possible long-term changes, its convenience sample, and no control group. Still, the originality of the theme must be highlighted. Therefore, future research should be carried out to analyze sleep disorders in individuals with CF and the association with other outcomes, such as quality of life and functional capacity.

Sleep disorders in children with CF are only related to the clinical characteristic of nutritional status, especially in those with low weight, which reinforces the importance of evaluating and monitoring these outcomes by the multidisciplinary team to adapt the management of these conditions in an early and systematic manner.

REFERENCES

1. Santana NN, Chaves CRMM, Goncalves CP, Gomes Junior SCS. Factors Associated to quality of life in children and adolescents with cystic fibrosis. Rev Paul Pediatr. 2020;38:e2018397. doi: 10.1590/1984-0462/2020/38/2018397.
2. Elborn JS. Cystic fibrosis. Lancet. 2016;388(10059):2519-31. doi: 10.1016/s0140-6736(16)00576-6.
3. Shakkottai A, O'Brien LM, Nasr SZ, Chervin RD. Sleep disturbances and their impact in pediatric cystic fibrosis. Sleep Med Rev. 2018;42:100-10. doi: 10.1016/j.smrv.2018.07.002.
4. Cohen-Cymberknoh M, Atia O, Gileles-Hillel A, Kerem E, Reiter J. Sleep disorders in patients with primary ciliary dyskinesia, cystic fibrosis with and without pancreatic insufficiency. Respir Med. 2019;151:96-101. doi: 10.1016/j.rmed.2019.03.022.
5. Íscar-Urrutia M, Madrid-Carbajal CJ, Rubinos-Cuadrado G, Fernández-Álvarez R, Vásquez-López MJ, Hernández-González C, et al. Objective and subjective sleep efficiency in adult patients with cystic fibrosis and impact on quality of life. Lung. 2018;196(6):761-7. doi: 10.1007/s00408-018-0167-x.
6. Reiter J, Gileles-Hillel A, Cohen-Cymberknoh M, Rosen D, Kerem E, et al. Sleep disorders in cystic fibrosis: a systematic review and meta-analysis. Sleep Med Rev. 2020;51:101279. doi: 10.1016/j.smrv.2020.101279
7. Lumertz MS, Pinto LA. Sleep-disordered breathing in cystic fibrosis pediatric subjects. Sleep Sci. 2019;12(3):165-70. doi: 10.5935/1984-0063.20190079

8. Kanga J, Kuhn R, Craigmyle L, Haverstock D, Church D. Cystic fibrosis clinical score: A new scoring system to evaluate acute pulmonary exacerbation. Clin Ther. 1999;21(8):1343-56. doi: 10.1016/s0149-2918(99)80035-6.

9. Ramsey BW. Management of Pulmonary Disease in Patients with Cystic Fibrosis. N Engl J Med. 1996;335(15):1167. doi: 10.1056/nejm199610103351522.

10. Nunes ML, Kampff JPR, Sadeh A. BISQ Questionnaire for Infant Sleep Assessment: translation into brazilian portuguese. Sleep Sci. 2012;5(3):89-91.

11. Ferreira VR, Carvalho LBC, Ruotolo F, Morais JF, Prado LB, Prado GF. Sleep disturbance scale for children: translation, cultural adaptation, and validation. Sleep Med. 2009;10(4):457-63. doi: 10.1016/j.sleep.2008.03.018.

12. BVS. Biblioteca Virtual em Saúde. Atenção primária à saúde. Programa Nacional Telessaúde Brasil Redes. Cálculo do Índice de Massa Corporal (MC) [Internet]. 2009 [cited 2009 jul 7]. Disponível em: http://aps.bvs.br/apps/calculadoras/?page=7.

13. Beydon N, Davis SD, Lombardi E, Allen JL, Arets HGM, Aurora P, et al. An Official American Thoracic Society/European Respiratory Society Statement: pulmonary function testing in preschool children. Am J Resp Crit Care Med. 2007;175(12):1304-45. doi: 10.1164/rccm.200605-642st

14. Manual IOS- Jaeger Impulse Oscillometry. Measurement Program IOS basic1e. cap. 15, p. 1-28. Versão 5.2.

15. Assumpcão MS, Goncalves RM, Martins R, Bobbio TG, Schivinski CI. Reference equations for impulse oscillometry system parameters in healthy brazilian children and adolescents. Respir Care. 2016;61(8):1090-9. doi: 10.4187/respcare.04226.

16. Graham BL, Steenbruggen I, Miller MR, Barjaktarevic IZ, Cooper BG, Hall GL, et al. Standardization of Spirometry 2019 Update. An Official American Thoracic Society and European Respiratory Society Technical Statement. Am J Respir Crit Care Med. 2019;200(8):e70-88. doi: 10.1164/rccm.201908-1590ST.

17. Pereira CAC, Sato T, Rodrigues SC. Novos valores de referência para espirometria forçada em brasileiros adultos de raça branca. J Bras Pneumol. 2007;33(4):397-406. doi: 10.1590/S1806-37132007000400008

18. Athanazio RA, Silva Filho LVRF, Vergara AA, Ribeiro AF, Riedi CA, Procianoy ELFA, et al. Diretrizes brasileiras de diagnóstico e tratamento da fibrose cística. J Bras Pneumol. 2017;43(3):219-45. doi: 10.1590/s1806-37562017000000065.

19. Doershuk CF, Matthews LW, Tucker AS, Nudelman H, Eddy G, Wise M, et al. A 5 year clinical evaluation of a therapeutic program for patients with cystic fibrosis. J Pediatr. 1996;65(5):677-93. doi: 10.1016/s0022-3476(64)80152-9.

20. Carneiro GV, Oliveira FS, Pereira LA, Rezende ÉRMA, Gonçalves LCP, Azevedo VMGO. Association between phenotypic and genotypic characteristics and disease severity in individuals with cystic fibrosis. Rev Paul Pediatr. 2023;41:e2021286. doi: 10.1590/1984-0462/2023/41/2021286.

21. Vanden Branden SL, McMullen A, Schechter MS, pasta DJ, Michaelis RL, Konstan MW, et al. Lung function decline from adolescence to young adulthood in cystic fibrosis. Pediatr Pulmonol. 2012;47(2):135-43. doi: 10.1002/ppul.21526.

22. Calella P, Valerio G, Brodlie M, Donini LM, Siervo M. Cystic fibrosis, body composition, and health outcomes: a systematic review. Nutrition. 2018;55-56:131-9. doi: 10.1016/j.nut.2018.03.052.

23. Ararat E, Sonawalla A, Berlinski A, Tas E. Nutritional status between 5-10 years is associated with cystic fibrosis-related diabetes in adolescence. Pediatr Pulmonol. 2021;56(10):3217-22. doi: 10.1002/ppul.25572.

24. Barbosa RRB, Liberato FMG, Freitas Coelho P, Vidal PR, Carvalho RBCO, Donadios MVF. Sleep disordered breathing and markers of morbidity in children and adolescents with cystic fibrosis. Pediatr Pulmonol. 2020;55(8):1974-83. doi: 10.1002/ppul.24780.

25. Sousa LP, Liberato FMG, Vendrusculo FM, Donadio MVF, Barbosa RRB. Obstructive sleep apnea in children and adolescents with cystic fibrosis and preserved lung function or mild impairment: a systematic review and meta-analysis of prevalence. Sleep Med. 2021;88:36-43. doi: 10.1016/j.sleep.2021.09.017.

26. Moreau L, Crenesse D, Berthier F, Albertini M. Relationship between impulse oscillometry and spirometric indices in cystic fibrosis children. Acta Pediatric. 2020;98(6):1019-23. doi: 10.1111/j.1651-2227.2009.01246.x.

27. Wamosy RMG, Assumpção MS, Parazzi PLF, Ribeiro JD, Roesler H, Schvinski CIS. Reliability of impulse oscillometry parameters in healthy children and in children with cystic fibrosis. Int J Clin Pract.2020;75(4):e13715. doi: 10.1111/ijcp.13715.