Original Investigation / *Özgün Araştırma*

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Clinical Manifestations and Diagnosis of Extrapulmonary Tuberculosis in Children

Akciğer Dışı Tüberkülozu Olan Çocuklarda Klinik Bulgular ve Tanı

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Abstract

Objective: Tuberculosis (TB) is an important public health problem both in developing and developed countries due to migration with increasing incidence despite control strategies. Various clinical manifestations of extrapulmonary tuberculosis (EPTB) cause delay in diagnosis and treatment. In the present study, we aimed to evaluate the clinical and laboratory findings of extrapulmonary tuberculosis in childhood.

Material and Methods: The medical records of patients hospitalized with the diagnosis of EPTB in the pediatric infection disease department between December 2007 and December 2017 were evaluated retrospectively.

Results: There were 90 patients diagnosed with EPTB with fifty-six (62.2%) female and 34 (37.8%) male patients. Age distributions ranged from 3 to 204 months and mean patient age was 123.2 ± 63.5 months. Twenty-nine (32.2%) patients had TB lymphadenitis, 14 (15.6%) had gastrointestinal TB, 12 (13.3%) had TB meningitis, 12 (13.3%) had miliary TB, 10 (11.1%) had pleural TB, and 6 (6.7%) patients had bone TB. Out of 7 patients (7.7%), three had renal, two had skin and the other two had genitourinary and pericarditis involvement. Nineteen patients had (21.1%) concomitant pulmonary involvement. Forty-one (45.6%) patients had history of TB contact. Forty-eight (53.3%) families received minimum wage. Eighty-seven (96.7%) patients had BCG vaccine, and the weight of 37 (41.1%) patients was below the third percentile. Forty-four (48.9%) patients had tuberculine skin test and 31 (34.4%) patients had interferon gamma release test positivity. Acid resistant bacteria was demonstrated in 29 (32.2%) of the body fluid samples and culture positivity was demonstrated in 28 (31.1%) samples. Histopathological findings were confirmed in 46 (51.1%) patients. When the patients with EPTB were

Öz

Giriş: Tüberküloz (TB), hem gelişmekte olan hem de göç nedeniyle gelişmiş ülkelerde, kontrol stratejilerine rağmen insidansı artan önemli bir halk sağlığı sorunudur. Akciğer dışı tüberküloz (ADTB)'un klinik belirtilerinin çok farklı olması tanı ve tedavide gecikmelere neden olmaktadır. Çalışmamızda çocukluk yaş grubunda ADTB tanısı alan olguların klinik ve laboratuvar bulgularının değerlendirilmesi amaçlanmıştır.

Gereç ve Yöntemler: Aralık 2007-Aralık 2017 tarihleri arasında fakültemiz çocuk enfeksiyon servisinde ADTB tanısıyla yatırılan hastaların tıbbi kayıtları geriye dönük olarak araştırmanın amaçları doğrultusunda olarak incelendi.

Bulgular: ADTB tanısı alan 90 hastanın 56 (%62.2)'sı kız, 34 (%37.8)'ü erkekti. Yaş ortalamaları 123.2 ± 63.5 aydı (3-204 ay). Olguların 29 (%32.2)'u TB lenfadenit, 14 (%15.6)'ü gastrointestinal TB, 12 (%13.3)'si TB menenjit, 12 (%13.3)'si miliyer TB, 10 (%11.1)'u plevra TB, 6 (%6.7)'sı kemik TB tanısı almıştı. Yedi (%7.7) hastanın üçünde böbrek, ikisinde deri tutulumu vardı, diğer ikisinde genitoüriner sistem ve perikart tutulumu vardı. On dokuz (%21.1) olguda akciğer tutulumu eşlik ediyordu. Olgularımızın 41 (%45.6)'inde TB teması vardı, 48 (%53.3)'inin ailesi asgari ücretle geçinmekteydi. Seksen yedisi (%96.7) Bacille Calmette Guerin (BCG) aşılıydı, 37 (%41.1)'sinin kilosu 3. persentilin altındaydı. Kırk dördünde (%48.9) tüberkülin deri testi (TDT) ve 31 (%34.4)'nde interferon gama salınım testi (İGRA) pozitifliği saptandı. Vücut sıvılarından alınan örneklemelerin 29 (%32.2)'unda aside dirençli bakteri tespit edildi, 28 (%31.1) örnekte kültürde üreme saptandı. Kırk altı (%51.1) olguda histopatolojik bulgular tanıyı doğruladı. ADTB olguları yerleşim bölgelerine göre kendi aralarında

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subgrouped according to localisations, ages of the patients with pleural TB were older (p= 0.005). Miliary TB was higher in families receiving minimum wage and in families with a history of TB contact (p= 0.000, p= 0.020 respectively). Miliary TB was more common in patients with body weights below the third percentile (p= 0.003). TDT positivity was higher in TB lymphadenitis (p= 0.010). Histopathologic findings were strongly positive in gastrointestinal TB (p= 0.000).

Conclusion: TB is an infectious disease that involves mostly the lymph nodes other than the lung. Although histopathologic and microbiologic evaluations are important in the diagnosis of EPTB, TB should be kept in mind in patients admitted with different complaints and signs in places with high TB incidence like our country.

Keywords: Child, extrapulmonary, tuberculosis

karşılaştırıldığında plevra TB'li hastaların yaşları daha yüksekti (p= 0.005). Miliyer TB asgari ücretle geçimini sağlayan ve TB teması olanlarda anlamlı olarak daha fazlaydı (p= 0.000, p= 0.020). Miliyer TB'de düşük vücut ağırlığı daha sıktı (p= 0.003). Olumlu TDT sonucu, tüberküloz lenfadenitli olgularda daha fazla idi (p= 0.010). Histopatolojik bulgular gastrointestinal sistem TB'sinde tanıyı anlamlı oranda destekledi (p= 0.000).

Sonuç: TB akciğer dışında en sık lenf düğümlerini tutmakla birlikte tüm organ ve dokuları tutabilen bir enfeksiyon hastalığıdır. Akciğer dışı tüberküloz tanısında histopatolojik veya mikrobiyolojik değerlendirme önemli olmakla birlikte ülkemiz gibi TB insidansının yüksek olduğu bölgelerde farklı şikayet ve bulgularla başvuran hastaların ayırıcı tanısında mutlaka hatırlanmalıdır.

Anahtar Kelimeler: Çocuk, akciğer dışı, tüberküloz

Introduction

Tuberculosis (TB) is still an infectious disease threatening human health. One fourth of the world population is infected with TB and still 5000 people die daily. World Health Organization (WHO) estimates that tuberculosis developed in 10.4 million people in 2015; however, the number of cases reported is only 6 million (1). This report reflects the fact that nearly more than half of the TB cases are not diagnosed or reported. Primary and postprimary TB show differences as regards age, histopathology, organ involvement, genetic liability, the immune system of the host, and clinical course. Although *Mycobacterium tuberculosis* primarily causes disease in the lungs by infiltrating through the respiratory tract, it is a very successful agent in postprimarily involving nearly all organs and tissues without discriminating any. Due to the fact that lymphohematogenous dissemination risk is high in children, extrapulmonary TB is more frequently seen. The probability of the infection turning into a disease increases as the host's age gets younger since the rate of dissemination rises with the decrease in patient age (2-5).

Lymph node and central nervous system tuberculosis are the most commonly observed extrapulmonary TB. TB can develop in the gastrointestinal system, bone-joint, cardiovascular system, genitourinary system and in the adrenal gland, skin and all other tissues. The fact that the clinical symptoms of extrapulmonary TB in childhood are not very distinctive and specific and that the sensitivity of immunologic and microbiologic tests is low cause delays in diagnosis and treatment. WHO has reported extrapulmonary tuberculosis (EPTB) in 0.8 million people the same year; however, the global impact of childhood EPTB is not known as a result of the limitations in diagnosis and reporting. Therefore, this study aimed at examining the clinical and laboratory findings of the cases diagnosed with EPTB during childhood.

Materials and Methods

The data of all patients admitted to the Pediatric Infectious Diseases Department of İstanbul University Cerrahpaşa Medical School between December 2007 and December 2017 with a diagnosis of extrapulmonary tuberculosis were retrospectively reviewed through patient files and electronic record systems. The patients were evaluated for age, gender, socioeconomical level, underlying disease, vaccination status, history of contact, involved areas, clinical manifestations, tuberculin skin test (TST) results, interferon gamma release test (IGRA) results, culture positivity, and laboratory and radiologic findings. TB diagnosis was made by history of familial TB and contact, clinical symptoms, TST and IGRA, lung graphy, computerized tomography, evaluation of body fluid samples and growth in culture specimen.

Fasting gastric juice, sputum, cerebrospinal fluid, urine, thoracentesis and paracentesis fluids and biopsy materials in lymphadenopathies are used for microbacterial culture. The cultures were examined in the Laboratory of the Microbiology Department of our faculty. Löwenstein-Jensen medium and Bactec medium were used in culture examinations, and all patients were evaluated in terms of Ehrlich Ziehl Neelsen (EZN) positivity. Reports of the Pediatric Radiology Department of the Radiology Department were grounded on in the evaluation of radiological findings.

The identification and classification of the patients were carried out according to the Tuberculosis Diagnosis and Treatment Guideline of the Ministry of Health. Patients with histologic and clinical findings concordant with tuberculosis or those that can show acid-resistant bacteria (ARB) in samples taken from organs other than the lung parenchyma were identified as EPTB. Pleura TB was recorded as EPTB, and patients with pleura TB whose sputum dissemination was found positive were evaluated as pulmonary and extrapulmonary TB.

SPSS program (downloaded from the official site of istanbul.edu.tr, version 21.0, IBM Company, SPSS Inc.) was used for statistical analysis. Numerical data were given as mean ± standard deviation and categorical variables were given as frequency (n) and percentage (%). One-way ANOVA was used in the evaluation of statistical significance of numerical differences between the two groups. Pearson chi-square test was used in the evaluation of the relation between two nominal variables. Statistical significance was set as $p< 0.05$. Local ethics committee approval from our faculty (14.03.2018-29430533) and consent from the parents of our patients were received for the study.

Results

Among the ninety patients having received extrapulmonary tuberculosis diagnosis, 56 (62.2%) were females and 34 (%37.8) were males. Mean age of the patients was 123.2 ± 63.5 months (3-204 months). Twenty-nine (32.2%) patients had TB lymphadenitis, 14 (15.6%) had gastrointestinal TB, 12 (13.3%) had TB meningitis, 12 (13.3%) had miliary TB, 10 (11.1%) had pleural TB, and 6 (6.7%) patients had bone TB. Out of 7 patients (7.7%), three had renal, two had skin and the other two had genitourinary and pericarditis involvement. Pulmonary involvement accompanied in nineteen patients (21.1%). Tuberculosis contact was present in 41 of our patients (45.6%), and the family of 48 of our patients (53.3%) received minimum wage. Eighty-seven (96.7%) were vaccinated, and the weight of 37 (41.1%) of our patients was under the third percentile. Tuberculin skin test positivity was found in forty-four (48.9%) and interferon gamma release test positivity was found in thirty-one (34.4%) of our cases.

Laboratory findings were as follows: mean sedimentation 53.324 ± 32.638 mm/h, mean C-reactive protein 4.422 ± 5.426 mg/dL, mean leukocyte count 14.001±19.002/mm^3, mean neutrophil count 7348 ± 4865/mm^3, mean lymphocyte count 2658 ± 1730/mm^3, mean thrombocyte count 360.108 ± 154.391/mm^3, and mean hemoglobin count 11.1 ± 1.6 g/dL.

Acid-resistant bacteria was detected in 29 (32.2%) of the samples taken from body fluids, no growth occurred in culture studies in 28 samples (31.1%), and isoniaside resistance was detected in 6 (6.7%) of the growths. Histopathological findings confirmed diagnosis in forty-six (51.1%) cases. Radiological diagnosis was present in fifty-eight (64.4%) cases.

A chronic disease that would suppress the immune system or one of the immunodeficiency syndromes was detected in a total of 7 cases (7.8%) in the scan for underlying diseases. Four patients received immunodeficiency diagnosis, one for interferon gamma (INF-γ) receptor deficiency, two for chronic granulomatosis disease and one for hypogammaglobulinemia. One of the other three cases had chronic renal insufficiency receiving hemodialysis and the other two had inflammatory bowel disease and juvenile idiopathic arthritis receiving immunosuppressive treatment. Patient demographics are shown in Table 1.

When 29 patients diagnosed with tuberculous lymphadenitis were classified with regard to localizations, there were 19 (65.5%) cervical, 5 (17.2%) axillary, 3 (10.3%) submandibular, and 2 (6.8%) submental lymphatic nodule involvement. TDT and IGRA positivity were determined in twenty-one (72.4%) and twelve (41.4%) patients, respectively. Growth was detected in the tissue samples of 7 patients (24.1%), one of which was isoniaside-resistant, and diagnosis was confirmed in 20 cases (68.9%) based on histopathological findings.

TST positivity was present in 8 (66.7%) patients and IGRA positivity was found in 3 (25.0%) patients in a total of 12 cases with tuberculous meningitis. Acid-resistant bacteria in the cerebrospinal fluid was found in five (41.7%) of our cases and culture positivity in 4 (33.3%).

Tuberculoma was detected in seven (58.3%) cases, basilar region involvement in three (25%) and hydrocephaly in one (8.3%); and there was no radiological finding in one case. None of our cases with tuberculous meningitis died.

When EPTB cases were compared as regards localizations, it was found that patients with pleura TB were older ($p= 0.005$). Miliary TB was seen significantly more in patients that earned minimum wage and was in contact with TB ($p= 0.000$, $p= 0.020$ respectively). Growth retardation was more

Table 1. Patient demographics

Total number of patients	**(n= 90) n (%)/Mean ± SD**
Gender	
Male	34 (37.8%)
Female	56 (62.2%)
Age distribution of the patients (month)	3-204 (123.2 ± 63.5)
Family history	41 (45.6%)
BCG vaccine	87 (96.7%)
Receiving minimum wage	48 (53.3%)
Growth retardation	37 (41.1%)
TST positivity	44 (48.9%)
IGRA positivity	31 (34.4%)
Infiltration in the lung parenchyma	19 (21.1%)
Histopathological diagnosis	46 (51.1%)
Radiologic diagnosis	58 (64.4%)
Accompanying disease	7 (7.8%)
Acid-resistant bacteria presence	29 (32.2%)
Culture growth	28 (31.1%)
Drug resistance	6 (6.7%)

BCG: Bacile Calmette Guerin, TST: Tuberculine skin test, IGRA: Interferon gamma release test.

Table 2. Subgroup comparison of extrapulmonary tuberculosis as regards localizations

	Lymphadenitis (n= 29)	GIT (n= 14)	Meningitis (n= 12)	Miliary (n= 12)	Pleurisy (n= 10)	Other (n= 13)	p
Gender (male)	20 (68.9%)	8 (57.1%)	8 (66.7%)	7 (58.3%)	7 (70.0%)	6 (46.2%)	0.765
Age (month)	138.2 ± 52.5	129.9 ± 57.8	91.0 ± 68.0	91.5 ± 74.3	175.1 ± 18.9	101.7 ± 71.1	0.005
Family history	13 (44.8%)	7 (50.0%)	6 (50.0%)	10 (3.3%)	1 (10.0%)	4 (30.8%)	0.020
Minimum wage	8 (27.6%)	10 (71.4%)	8 (66.7%)	12 (100%)	5(50.0%)	5 (38.5%)	0.000
Growth retardation	3 (10.3%)	9 (64.3%)	5 (41.7%)	10 (83.3%)	6 (60.0%)	4 (30.8%)	0.003
TST positivity	21 (72.4%)	5 (35.7%)	8 (66.7%)	4 (33.3%)	2 (20.0%)	4 (30.8%)	0.010
IGRA	12 (41.4%)	6 (42.9%)	3 (25.0%)	4 (33.3%)	5 (50.0%)	1 (7.7%)	0.242
Accompanying disease	0 (0%)	0 (0%)	2 (16.7%)	1 (8,3%)	2 (20.0%)	2 (15.3%)	0.152
ARB	7 (24.1%)	4 (28.6%)	5 (41.7%)	6 (50.0%)	3 (30.0%)	4 (30.8%)	0.667
Growth	7 (24.1%)	6 (42.9%)	4 (33.3%)	7 (58.3%)	3 (30.0%)	1 (7.7%)	0.106
Resistance	2 (6.9%)	1 (7.1%)	2 (16.7%)	1 (8.3%)	0 (0%)	0 (0%)	0.603
Histologic diagnosis	20 (68.9%)	12(85.7%)	3 (25.0%)	4 (33.3%)	0 (0.0%)	7 (53.8%)	0.000

GIT: Gastrointestinal tract, TST: Tuberculin skin test, IGRA: Interferon gamma release test, ARB: Acid-resistant bacteria.

frequently observed in miliary TB (p= 0.003). Positive TST was more in cases with tuberculous lymphadenitis (p= 0.010). Histopathological findings significantly supported diagnosis in gastrointestinal tract tuberculosis (p= 0.000). Comparison of EPTB as regards localizations is shown in Table 2.

In 71.1% (n= 64) and 28.4% (n= 26) of the cases, tetrad and triad TB treatments were started respectively by considering the clinical picture and risk factors. Streptomycin in 50 cases (78.1%) and ethambutol in 14 cases (21.8%) were preferred as the fourth drug. As a drug side effect during treatment, temporary liver enzyme elevation was observed in 8 (%8.8) patients and uric acid elevation in 6 (6.6%), but there was no need to terminate treatment. No patient developed autotoxicity related to streptomycin. One patient with gastrointestinal TB had ileus attack seven times during the course of treatment and was perforated from the ileocecal region in the ninth month of treatment. The patient was operated and applied with ileocolic anastomosis and temporary colostomy was made. No complications developed in other patients and none died.

Discussion

The fight of humankind with TB that has been infecting people since 300 million years is still going on (6,7). Worldwide, tuberculosis ranks first among infectious diseases that lead to mortality from one contagious agent. According to the 2017 report of World Health Organization, 1.7 million people died as a result of TB infection in 2016 (8). Despite official politics and control efforts to prevent tuberculosis, TB is still a lethal health problem due to the difficulties in diagnosis and the fact that TB does not have a standard case identification. TB bacillus that infiltrates the body through the respiratory tract or other different routes, even if rarely spreads to different tissues of the body through lymphohematogenous way and leads to organ involvement. In consequence of the fact that probability of lymphohematogenous dissemination is higher in children, EPTB is seen more in children than in adults (9,10). Superficial lymph node involvement is the most commonly seen clinical form of EPTB in children. TB lymphadenitis is seen more in the childhood period in regions with a high TB incidence rate and in females in the 20-40 age group in regions with low TB incidence rate. In a study carried out in regions where TB is highly endemic, lymph node TB has been reported as the most common extrapulmonary involvement of TB (11,12). Again, in a study conducted in Colombia, TB lymphadenitis has been reported as the most frequently seen EPTB with a rate of 40.6% in children (13). In our study group, lymphadenitis was detected as the most frequently seen EPTB with a rate of 32.2%. Tinsa et al. have similarly reported the frequency of TB lymphadenitis at a rate of 35% (14). Slow-growing, painless, rigid lymphadenopathy is its most important clinical finding, and it most frequently localized in the cervical region with a changing rate of 63-77% (15,16). As consistent with the literature, most frequently observed localization in our cases was the cervical lymph nodes (65.5%) followed by axillary (17.1%), submandibular (%10.3) and submental lymph node (%6.8) involvement. Diagnosis of tuberculous lymphadenitis in 20 cases was proven by histopathological findings.

EPTB cases aside from TB lymphadenitis respectively received gastrointestinal TB, meningitis, miliary TB, TB pleurisy, and bone TB diagnosis. There are studies reporting the most frequent form of EPTB as lymphadenitis and gastrointestinal TB (17-19). In a study conducted in our country, the most common EPTB forms in children have been reported respectively as lymphadenopathy, bone, meninx and miliary TB (20). In another study conducted in children, involvement regions apart from TB lymphadenitis have been found as the central

nervous system (13%), pleura (6%), miliary (5%), ad bone TB (4%), respectively (12).

Adult contact with active disease is a vital approach in detecting TB in children. Contact rate is between 25% and 66% in various studies (21,22). Forty-one cases (45.6%) in our study had contact. Contact with father was detected in 50% of the cases. Contact was higher in miliary TB cases (p= 0.020). Reported rates of contact for our country is between 16% and 23.7% (20,23).

BCG, which is the first developed TB vaccine that is still used, is known to improve cellular immunity and thus, protects against disseminated tuberculosis. Eighty seven (96.7%) of our cases contracted TB even though they were vaccinated; however, there was no patient who died or became disabled from TB.

TST is the mainly used examination in TB scanning in our country. However, the fact that TST is affected by many factors including the BCG vaccine, immunity of the individual and application and interpretation technique results in low sensitivity and specifity. Not with standing, sensitivity and specifity of IGRA are very high. In our cases, 48.9% TST and %34.4% IGRA positivity were detected. TST positivity in childhood EPTB scanning varies at a rate of 52-69.6% (21). Studies investigating the positivity of interferon gamma release tests in childhood EPTB are limited, and Shin et al. have reported IGRA positivity at a rate of 64.3% in a study conducted on adult patients with EPTB (24).

Detection of mycobacteria in clinical samples is the gold standard method in diagnosing tuberculosis. The ARB method used in early diagnosis gives fast results. However, the presentation of bacillus in childhood TB is not always possible and culture positivity is at a lower rate contrary to adults. Moreover, the fact that patients with EPTB have a small number of bacilli and technical difficulties arise from time to time during sampling makes bacteriological confirmation very difficult. In many studies, culture positivity changes between 10-40% (25-27). In our study, acid-resistant bacteria was detected in 29 children (32.2%) and bacillus could be grown in culture in 28 samples (31.1%). In studies published from our country, culture positivity varies between 23.5%-31% (28,29).

It is important to determine drug sensitivity of the bacillus grown form the source that the case came in contact with in the planning of childhood TB treatment. Recently, there has been an increase in multiple resistance development in adult cases, which leads to a major problem in the treatment of children who were in contact. 2.2%-7.9% resistance is reported in pediatric patients in our country (29). Similarly, in our study, drug resistance was detected in 6 (6.7%) of the growths and they were all resistant to single isoniaside.

Drugs that could penetrate into different fluids and tissues should be preferred in the treatment of childhood extrapulmonary tuberculosis. Children tolerate high doses of drugs better and side effects are seen at a lower rate. 71.1% of our cases received tetrad and 28.4% received triad anti-TB treatment. As the fourth drug, streptomycin was preferred in 78.1% of the cases and ethambutol in 21.8% of the cases. Similar to our study, Guleç et al. have preferred streptomycin in 79% of the cases and ethambutol in 21% as the fourth drug (30). No drug side effect was seen in our patients apart from temporary liver enzyme elevation and uric acid elevation, and visual fields and auditory tests were found normal during follow-up. Mortality rate was observed as 0% in our cases and no disability developed apart from learning disability that developed in two cases. Ileocecal perforation occurred in the ninth month of the treatment in one patient with gastrointestinal tuberculosis diagnosis. Bowel perforation has been reported in elderly patients with accompanying severe diseases; however, perforation in children especially in the advanced months of treatment is very rare.

Worldwide, tuberculosis is a disease in societies with low income rates and socioeconomic levels. In our study, 53.3% of the families received minimum wage and miliary TB was higher in these families (p= 0.000). Malnutrition and low body weight are commonly accompanying findings of TB. The weight of 37 (41.1%) of our patients was below third percentile and low body weight was more frequently observed in miliary TB (p= 0.003). We are of the opinion that low income levels have an effect on weight loss and low body weight besides inflammatory cytokines like elevated IFN-γ and IL-10 during the course of tuberculosis infection.

In conclusion, together with involving lymph nodes apart from the lungs during childhood, tuberculosis is an infectious disease involving all organs and tissues. 96.7% of the patients had TB despite vaccination and TB contact was found at a rate of 45.6%. Gold standard in diagnosis is the growth of bacillus in culture. Diagnosis of extrapulmonary tuberculosis was proven by the growth of 31.2% bacilli in culture and by 51.1% histopathological findings. Rate of resistant bacillus was 6.7%. Mortality rate of our patients was 0% and disability rate was very low (2/90). In light of these data, tuberculosis must be investigated in the differential diagnosis of the patients presenting with varying complaints and findings in regions where TB incidence is high, like our country. Apart from being clinically challenging, tuberculosis is a preventable and treatable disease.

Ethics Committe Approval: Consent from all parents of our patients and approval from the local ethics committee of our faculty (14.03.2018-29430533) were received for the study.

Informed Consent: Inform consent was taken from the parents of children.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - YC, DA, HC, NA; Design - DA, YC, HC, NA; Supervision - YC, HC; Materials - DA, YC, HC, NA; Data Collection and/or Processing - DA, YC, HC, NA; Analysis and/or Interpretation - DA, YC, HC; Literature Review - DA, YC; Writing - DA, YC; Critical Review - YC, HC, NA.

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