Research Article / Araştırma Makalesi

Clinical and Etiological Profile of Hospitalized Children with Pleural Effusion: A single Center Experience Between 2012-2022

Plevral Efüzyonla Hastaneye Yatan Çocukların Epidemiyolojik Ve Klinik Profili: Tek Merkez Deneyimi 2012-2022

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Özet: Plevral efüzyon, çocuklarda ciddi morbidite ve mortaliteye yol açması sebebiyle, bakteriyel pnömoninin önemli bir bir komplikasyonudur. Bu çalışmanın amacı, çocuklarda plevral efüzyonun epidemiyolojik ve klinik özelliklerinin araştırılmasıdır.Ocak 2012-Aralık 2022 tarihleri arasında Eskişehir Osmangazi Üniversitesi Tıp Fakültesi'nde izlenen plevral efüzyonlu çocukların tıbbi kayıtları retrospektif olarak değerlendirildi. Klinik ve etiyolojik özellikleri, laboratuvar ve radyoloji sonuçları ve tedavi rejimleri değerlendirildi. Yaşları 7 ila 216 ay (medyan 100 ay) arasında olan 59 çocuğun (%55,9'u kız) tıbbi kayıtları kaydedildi. Plevral efüzyon etiyolojisi; 37 çocukta (%62,7) parapnömonik efüzyon, sekiz çocukta (%13,5) tüberküloz plörezi idi. En yaygın bakteriyel patojenler Streptococcus pyogenes, Mycobacterium tuberculosis, Pseudomonas aeruginosa, Streptococcus pneumoniae ve Haemophilus influenzae idi. Pandemi sonrası dönemde tüberküloz plörezi vakaları azalırken, Streptococcus pyogenes'e bağlı plevral efüzyonlarda artış görülmektedir. Olguların %39'una tek başına medikal tedavi, %55'ine tüp torakostomi, %18,6'sına torakotomi ve dekortikasyon uygulandı. Çocukların %45,8'inin pediatrik yoğun bakım ünitesinde kalması gerekti. Medyan hastanede kalış süresi 12 gündü. Pediatrik plevral efüzyonların en sık nedeni bakteriyel ajanlara bağlı parapnömonik efüzyonlardır. COVID-19 pandemisinden sonra tüberküloz plörezi vakaları azalırken, Streptococcus pyogenes kaynaklı plevral efüzyon/ampiyemde artış görülmektedir.
Anahtar Kelimeler: Streptococcus pyogenes, Plevral efüzyon, Çocuk, iGAS, COVID-19 pnademi

Abstract: Pleural effusion is a complication of bacterial pneumonia that is of particular importance because of its significant morbidity and mortality in children. The aim of this study was to investigate the clinical and etiological profile of pleural effusion in children. Medical records of children with pleural effusion who were followed up at University Faculty of Medicine between January 2012 and December 2022 were retrospectively evaluated. Clinical and etiological features, laboratory and radiological results, and treatment regimens of were noted. Medical records of 59 children (55.9% girls) aged between 7 to 216 months (median 100 months) have been noted. The etiology of pleural effusion was parapneumonic effusion in 37 children (62.7%), tuberculous pleurisy in eight children (13.5%). The most common bacterial pathogens were Streptococcus pyogenes, Mycobacterium tuberculosis, Pseudomonas aeruginosa, Streptococcus pneumoniae and Haemophilus influenzae. In the early period of the COVID-19 pandemic, while cases of tuberculous pleurisy are decreasing, there is an increase in pleural effusions due to Streptococcus pyogenes. Medical treatment alone was given in 39% of cases, tube thoracostomy in 55%, thoracotomy and decortication in 18.6%. A 45.8% of children required pediatric intensive care unit stay. The median hospital stay was 12 days.
Conclusion: Parapneumonic effusions due to bacterial agents are the most common cause of pediatric pleural effusions. In the early period of the COVID-19 pandemic, while cases of tuberculosis pleurisy are decreasing, there is an increase in Streptococcus pyogenes-induced pleural effusion/empyema.
Keywords: Pleural Effusion, Pediatric, Streptococcus pyogenes, iGAS, COVID-19 pandemic

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1. Introduction

Pleural effusion is an abnormal accumulation of fluid between the visceral and parietal pleura and its etiology includes pneumonia, cardiac disease, rheumatological disease, renal disease and hematological disease(1). Pneumonia, which is an important cause of pleural effusion, is a group of diseases with high mortality and morbidity. According to the World Health Organization, 156 million children under the age of 5 are diagnosed with pneumonia each year, and pneumonia is responsible for approximately 42% of childhood deaths (2-5). Although the incidence of pleural effusion has decreased significantly with the effective use of vaccination strategies and antibiotics, parapneumonic effusion (PPE) still occurs in 2-40% of hospitalised patients with bacterial pneumonia (4.5) .

Radiological methods and biochemical and microbiological tests of the pleural fluid play a key role in the diagnosis of pleural effusion and in determining its etiology. Pleural fluid and serum pH, protein, lactate dehydrogenase levels (LDH), glucose levels, direct microscopic examination and further microbiological tests including standard culture tests, polymerase chain reaction (PCR) should be investigated in the first stage (5,6). The etiological cause, the size and location of the pleural effusion and the degree of respiratory distress will guide the choice of treatment6. Medical management, thoracentesis, tube thoracostomy, video-assisted thoracoscopic surgery (VATS), intrapleural fibrinolytic therapy, surgical thoracotomy and decortication are the main treatment modalities.

The aim of this retrospective study was to evaluate the clinical and etiological characteristics, of children with pleural effusions.

2. Materials and Methods

Medical records of pediatric patients followed up for pleural effusion at University Faculty of Medicine between January 2012 and December 2022 were included in the study. The study protocol was approved by University Local Ethical Committee (20 June 2023/67).

Age, gender, presence of underlying disease, symptoms and clinical findings at admission, laboratory and radiological imaging results have been noted. Biochemical and microbiological laboratory results of pleural fluid, type of bacteriological agent detected in pleural fluid, exudate transudate character of pleural fluid, medical and surgical treatment modalities, and prognosis were noted. While the first case with COVID-19 have been reported in March 2020 in Turkiye, the pandemic period was considered after this date.

Light's criteria were used to differentiate transudate/exudate and to diagnose empyema. Pleural/serum protein > 0.5, pleural/serum LDH > 0.6, pleural LDH > 2/3 of the upper limit of normal serum LDH (or LDH>200 IU/L) are criteria. If at least one of these criteria was present, it was considered to be exudate(7). For empyema; glucose <40 mg/dl, LDH >1000 IU/L, pH<7.2 were accepted as criteria. Microbiological tests such as direct microscopic examination, acid-fast staining, culture, multiplex polymerase chain reaction (PCR) and tuberculosis PCR were studied to detect the etiological agent from pleural fluid samples. The Biofire Filmarray Pneumonia panel plus kit (Biomerieux, France) was used for pleural fluid testing in selected cases.

The Statistical Package for Social Sciences (SPSS) version 28.0 for Windows (SPSS, Chicago, IL, USA) was used for statistical analysis. Continuous variables were expressed as median (minimum-maximum). After assessing normal distribution using the Kolmogorov-Smirnov test, parameters were compared between groups using the Mann-Whitney U test for continuous variables and the chi-squared test for categorical variables. p values < 0.05 were considered statistically significant.

3. Results

Medical records of 59 children (55.9% girls) aged between 7 to 216 months (median 100 months) have been noted. Twenty-one children (35%) had an underlying condition;

most commonly rheumatological (10%), followed by neurological (8.4%), haematological (6.7%), cardiac (5%) causes. The most common presenting symptoms were fever (83.1%), cough (81.4%), respiratory distress (69.5%) and chest pain (54.2%) (Table 1).

The etiology of pleural effusion was parapneumonic effusion in 37 children (62.7%), tuberculous pleurisy in eight children (13.5%), rheumatological diseases in six children (three children with systemic lupus erythematosus, two children with multisystemic inflammatory syndrome (MIS-C), one child with polyarthritis nodosa) four children with cardiac diseases (restrictive cardiomyopathy, constrictive pericarditis, supraventricular tachycardia, heart failure), two children with renal disease (chronic renal failure, nephrotic syndrome), one child with hemophagocytic lymphohistiocytosis (Table 1).

Chest radiography was performed in all cases, computed thorax tomography were performed in 55% of children. Pleural effusion was present in the right lobe in 35.6%, in the left lobe in 33.9% and bilaterally in 30.5% of cases. Pericardial effusion was present in 17% of cases, pneumothorax in 3.4% and pulmonary embolism in 1.7% (Table 1).

In laboratory tests of 35 cases where pleural fluid samples could be obtained, 34% of cases were purulent, 28% were haemorrhagic, 14% were yellow and 3% were chylothorax. According to Light's criteria, pleural/serum protein was >0.5 in 15 (42%) cases, pleural/serum LDH >0.6 in 16 (45%) cases and pleural LDH >200 u/l in 14 (40%) cases (Table-2). While 80% of the pleural fluid samples of the cases were exudate, (Table-2).

42% of the cases were defined as empyema. Most cases of empyema were located in the right lobe. There was no difference between cases with and without empyema, intensive care admission and surgical treatment (Table-3). While cases with empyema were mainly due to parapneumonic, cases without empyema were mainly due to rheumatological, cardiac and renal diseases ($p<0.05$) (Table-3).

Eight children (18%) had tuberculous pleurisy and seven out of these eight children cases were in the pre-pandemic period (Table-4). *Mycobacterium tuberculosis* was detected by culture in two children and by PCR in two children. Bacterial pathogens were detected in 19 cases by at least one of culture and multiplex PCR testing of pleural fluid. Pathogens were detected by culture in 11 cases, by multiplex PCR in 17 cases and by both culture and PCR in 10 cases (Table-4). *Streptococcus pyogenes* was detected in five children (11%), *Acinotobacter baumanni* in three children, *Pseudomonas aeuriginosa* in three children (6.6%), *Haemophilus influenzae* in two children (4.4%), *Streptococcus pneumoniae* in two children (4.4%) (Table 4). All five cases with *Streptococcus pyogenes* were in the pandemic period. The most common viral pathogens were as follows: rhino-enterovirus (8.8%), human metapneumovirus (4.4%) and adenovirus (2.2%).

While medical management alone was used in 39% of cases, chest tube thoracostomy was used in 55% of cases, thoracotomy and decortication in 18.6% of cases. The chest tube remained in place for 3-7 days in 27.1% of cases, 7-14 days in 13.6% of cases, and >14 days in 15.3% of cases. The mean hospital stay was 12 days and 45.8% children required pediatric intensive care unit stay. Mortality have been reported in six children (%10.1).

Table-1. Clinical Characteristics of 59 Children with Pleural Effusion

		Gender	
Age (month)	100 (7-216)	Girl	33 (55.9)
		Boy	26 (44.1)
Chronic Disease	21 (35)	Etiology	
Rheumatologic	6 (10)	Parapneumonic	37 (62.7)
Neurologic	5 (8.4)	Tuberculosis Pleurisy	8 (13.5)
Hematologic	4 (6.7)	Rheumatology	6 (10.2)
Cardiac	3 (5)	Cardiac	4 (6.8)
Renal	2 (3.3)	Renal	2 (2.4)
Gastrointestinal	2 (3.3)	Hematologic	1 (1.7)
Diabetes Mellitus	1 (1.6)	Genetic (Gorham Syndrome)	1 (1.7)
Symptoms – Signs		Laboratory Findings	
Fever	49 (83.1)	Leukocytosis	33 (56)
Cough	48 (81.4)	Acute phase reactants ↑	45 (76)
Tachypnea	42 (71.2)	Pleural Fluid	35 (61)
Dyspnea	41 (69.5)	Exudate	28 (49)
Chest Pain	32 (54.2)	Transude	7 (12)
Cyanosis	27 (45.8)	Empyema	15 (25)
Intensive Care	27 (45.8)	Pericardial Effusion	10 (17)
		Pneumothorax	2 (3.4)
		Embolism	1 (1.7)
Effusion Location		Radiological Imaging	
Right Lobe	21 (35.6)	Chest X-ray	59 (100)
Left Lobe	20 (33.9)	Computed Tomography	33 (55)
Bilateral	18 (30.5)		
Treatment		Tube Removal Time	
Medical (only)	23 (39)	3-7 days	16 (27.1)
Thoracentesis	5 (8.5)	7-14 days	8 (13.6)
Tube Thoracostomy	33 (55)	>14 days	9 (15.3)
Thoracotomy/Decortication	11 (18.6)		
VATS	1 (1.6)		
Length of Stay (day)	12 (3-41)	Mortality	6 (10.2)

Table 2. Characteristic and laboratory finding of pleural fluid samples (n=35)

Color	
Purulent	12 (34)
Hemorrhagic	10 (28)
Light (Clear)	7 (20)
Yellow	5 (14)
Chylothorax	1 (3)
Glucose*	
<40 mg/dl	6 (17)
40-60 mg/dl	1 (2.8)
>60 mg/dl	15 (42)
LDH*	
<200 u/l	4 (11)
>200 u/l	14 (40)
>1000 u/l	9 (25)
pH	
<7.2	6 (17)
>7.2	5 (14)
Lights' Criteria	
Pleural/serum protein>0.5	15 (42)
Pleural/serum LDH>0.6	16 (45)
Pleural LDH >200 u/l	14 (40)
Exudate	28 (80)
Empyema	15 (42)

**Because the samples were insufficient and small, LDH from 7 samples, glucose from 13 samples were not studied.*

Table- 3. Clinical characteristics of 35 children with obtained pleural fluids

	Empyema n=15	**Non-Empyema N=20**	**Total N=35**	**p**
Prepandemic	8 (38)	13 (62)	21	
Pandemic	7 (50)	7 (50)	14	ns
Hospitalization				
Intensive Care	10 (53)	9 (47)	19	ns
Ward	5 (31)	11 (69)	16	
Involvment				
Right Lobe	7 (70)	3 (30)	10	
Left Lobe	5 (42)	7 (58)	12	**p<0.05**
Bilateral	3 (23)	10 (77)	13	
Etiology				
Parapneumonic	13 (48)	14 (52)	27	
Rheumatology	-	4 (100)	4	**ns**
Cardiac	-	1 (100)	1	
Renal	-	1 (100)	1	
Hematological	1 (100)	-	1	
Genetics	1 (100)	-	1	
Lights' Criteria				
Pleural/serum protein>0.5	8 (53)	7 (47)	15	ns
Pleural/serum LDH>0.6	9 (56)	7 (44)	16	ns
Pleural LDH >200 u/l	9 (64)	5 (36)	14	**p<0.05**
Treatment				
Thoracentesis	2 (28)	5 (72)	7	
Tube-thoracostomy	10 (50)	9 (45)	19	ns
Thoracotomy/decortication	3 (37)	-5 (63)	8	
VATS	1 (100))		1	
Duration of thorax tube				
3-7 days	7 (58)	5 (42)	12	
7-14 days	2 (33)	4 (66)	6	ns
>14 days	4 (50)	4 (50)	8	
Yielded microorganisms				
Streptococcus pyogenes	4 (80)	1 (20)	5	
Mycobacterium Tuberculosis	1 (25)	3 (75)	4	
Acinetobacter baumannii	-	3 (100)	3	
Pseudomonas aeruginosa	-	3 (100)	3	*ns*
Streptococcus pneumoniae	2 (100)	-	2	
Haemophilus influenzae	2 (100)	-	2	
Klebsiella pneumoniae	-	2 (100)	2	
Mycoplasma pneumoniae	1 (100)	-	1	
Staphylococcus aureus	1 (100)	-	1	

**: non-significant*

Table- 4. Comparison of etiological factors before and during the COVID-19 pandemic

	Pre-pandemic n=36	**Pandemic n=23**	**Total N=59**
Tuberculosis	7 (87.5)	1 (12.5)	8
Streptococcus pyogenes	-	5 (100)	5
Acinetobacter baumanii	1 (33)	2 (67)	3
Pseudomonas aeruginosa	1 (33)	2 (67)	3
Streptococcus pneumoniae	1 (50)	1 (50)	2
Haemophilus influenzae	-	2 (100)	2
Klebsiella pneumoniae	-	2 (100)	2
Mycoplasma pneumoniae	1 (100)	-	1
Staphylococcus aureus	1 (100)	-	1
Rhinovirus/enterovirus	1 (25)	3 (75)	4
Human metapneumovirus	-	2 (100)	2
Adenovirus	-	1 (100)	1

4. Discussion

In this study, the most common causes of pleural effusion in children were parapneumonic, followed by tuberculous pleurisy. Parapneumonic effusion was the most common etiological cause in our study, in concordance with the literature, similarly, Kaplan et al.(7) reported that the most common causes of pleural effusion in children were parapneumonic effusion, sepsis, rheumatological and cardiac diseases(7). Utine et al. (8) reported that the most common causes of pleural effusion were parapneumonic effusion, tuberculosis and cardiac disease. In our study, pleural fluid samples were obtained in 35 children and the most common bacterial pathogens were, *Streptococcus pyogenes, Pseudomonas aeruginosa, Streptococcus pneumoniae and Haemophilus influenzae* and also *Mycobacterium tuberculosis*. Liese et al.(9) reported that the most common etiologies of paediatric pleural effusions were *S. pneumoniae, S. pyogenes and Staphylococcus aureus*. Krenke et al. (10) reported that *Streptococcus pneumoniae and Streptococcus pyogenes* were the most common aetiological pathogens. Kaplan et al.(7) and Utine et al.(8) reported that *S. pneumoniae and S. aureus* were the most common pathogens in pediatric pleural effusion.

In our study, contrary to the literature, the number of cases with *S. pyogenes* was higher. All *S. pyogenes* cases occurred in the pandemic period. This can be explained by the increase in invasive group A streptococcal (IGAS) infections in Turkiye and around the world, especially in England, France and Ireland, with the removal of isolation and social distancing measures in the pandemic period (11-15). Even during the pandemic, childhood vaccinations were strictly and regularly carried out in our country, and there was no decrease in vaccination rates(16). There was no increase in pathogens such as *S. pneumoniae and H. influenzae*.

One of the most common causes of pleural effusion was tuberculous pleurisy, and 7 out of 8 cases in our study were in the pre-pandemic period. As in the literature, we attributed the decrease in tuberculosis cases to the pandemic measures or to the decrease in hospital admissions. As in the literature, we attributed the decrease in tuberculosis cases in the early period of the COVID-19 pandemic due to the use of masks, isolation precautions, or the decrease in hospital admissions (17,18).

In our study, the rate of empyema (42%) was similar to that reported in the literature. Two different studies reported the rate of empyema in cases with pleural effusion to be 60.3% and 61.7% (8,19). *Staphylococcus aureus, S. pneumoniae and S. pyogenes* have been reported as the most common pathogens causing empyema in children(7-10,19-20). In our study, the pathogens were similar to those reported in the literature, although the rate of *Streptococcus pyogenes* was higher. Krenke et al. (10) reported that molecular methods were three times more successful in detecting pathogens than culture in patients with pleural effusion. In agreement with the literature, the detection rate of pathogens by PCR was higher in our study than by culture. This can be explained by the high sensitivity and specificity of molecular tests, the ability to detect many pathogens in a single sample, and the fact that they are less affected by antibiotic use than culture.

The Infectious Diseases Society of America (IDSA) guidelines recommend medical management and/or drainage for small and uncomplicated effusions that do not cause respiratory distress, and surgical management, VATS and intrapleural fibrinolysis for large and unresponsive effusions that cause respiratory distress (6). A recent study in Türkiye reported that 74% of children with pleural effusion underwent thoracentesis, 55% underwent tube thoracostomy, 5.5% underwent VATS and 2.7% underwent decortication(7). Another study showed that tube thoracostomy was performed in 84.3% of cases of pleural empyema (21). In our study, in parallel with the literature, the most common treatment modalities were tube thoracostomy and medical management. The rate of patients who underwent surgical thoracotomy and decortication was high (18.5%). This is due to the high rate of cases unresponsive to medical and drainage

methods and invasive infectious agents such *as Streptococcus pyogenes*.

The main limitations of our study are single center experience and limited number of cases. Pleural fluid samples cannot be obtained from all cases.

In conclusion, parapneumonic effusions are the most common cause of pediatric pleural effusions. Although the most common parapneumonic pathogens are vaccine-preventable agents such as *S. pneumoniae and H. influenzae*, invasive pathogens such as *Streptococcus pyogenes* should be considered. In the early period of the COVID-19 pandemic, while cases of tuberculous pleurisy are decreasing, there is an increase in *Streptococcus pyogenes*-induced effusions/empyemas. Although the first-line treatment is always medical treatment with drainage methods such as thoracentesis and tube thoracostomy, surgical methods such as thoracotomy and decortication should be considered, especially in cases that do not respond to these treatments.

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Etik Bilgiler
Etik Kurul Onayı: Çalışma Eskişehir Osmangazi Üniversitesi Girişimsel Olmayan Araştırmalar Etik Kurulu tarafından onaylanmıştır (Karar no: 67, Tarih: 20.06.2023).
Onam: Bu çalışma için katılımcılardan sözlü onam alınmıştır.
Telif Hakkı Devir Formu: Tüm yazarlar tarafından Telif Hakkı Devir Formu imzalanmıştır.
Hakem Değerlendirmesi: Hakem değerlendirmesinden geçmiştir.
Yazar Katkı Oranları: : "Fikir/kavram: GB,, MCK, MİN, YK,, Hİ, ÇÖ, TU, ÖK, EÇD. Tasarım: GB, YK, ÖK, EÇD. Veri Toplama: GB, MCK, YK. Veri İşleme: GB, EK, MCK, MİN, YK, MSA, Hİ, ÇÖ, TU, ÖK, EÇD. Analiz/Yorum: GB, YK, ÖK, EÇD. Literatür taraması: GB, YK, ÖK, EÇD. Yazma: GB, YK, ÖK, EÇD. "
Çıkar Çatışması Bildirimi: Yazarlar çıkar çatışması olmadığını beyan etmişlerdir.
Destek ve Teşekkür Beyanı: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.