

# A retrospective cohort study investigating the etiology of primary spontaneous pneumothorax in children: Radiological and genetic analysis

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## Ethics Committee Approval

The necessary permissions were obtained from the families and the institution for the study. The study was approved by the Balıkesir University Faculty of Medicine Clinical Research Ethics Committee (2021/259).

All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

## Conflict of Interest

No conflict of interest was declared by the authors.

## Financial Disclosure

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

## Published

2023 July 13

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Published by JOSAM

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## Abstract

**Background/Aim:** Spontaneous pneumothorax is a serious health concern due to its life-threatening nature. It occurs when air sacs in the lungs rupture, causing air to accumulate in the chest cavity and making normal breathing difficult. Primary spontaneous pneumothorax (PSP) refers to the accumulation of air in the pleural space without any traumatic or iatrogenic cause. The objectives of our study are to identify the predisposing factors in PSP patients, determine which patients should undergo genetic analysis, and present the results of a new treatment algorithm.

**Methods:** This study is a retrospective cohort analysis of children diagnosed with PSP and admitted to the emergency department or pediatric surgery clinic. The study evaluates demographic data, radiological findings, and molecular genetic analyses of these patients. Treatment planning was conducted using thoracic computed tomography (CT) or high-resolution computed tomography (HRCT) after the acute phase, and eligible patients were selected for genetic analysis based on syndromes commonly associated with PSP.

**Results:** The study included 14 patients, 10 boys and four girls, with an average age of 16.14 (0.95) years. PSP was detected on the right side in nine male patients and on the left side in one male patient, while in girls, it was detected on the right side in two patients and on the left side in two patients. Radiological findings included air cysts, fibrotic changes, and pleural thickening. Folliculin (FLCN) mutation was detected in two patients after genetic analysis.

**Conclusion:** In the stratified treatment protocol, radiological findings were used as a guide, and the detection of possible syndromic mutations by genetic analysis was deemed important for future management.

**Keywords:** primary spontaneous pneumothorax, video-assisted thoracic surgery, child, lung

## Introduction

Pneumothorax is a condition where air accumulates in the pleural cavity, causing partial or complete lung collapse. Spontaneous pneumothorax is a serious health concern due to its life-threatening nature. It occurs when air sacs in the lungs rupture, causing air to accumulate in the chest cavity and making normal breathing difficult. This condition is a medical emergency because increasing air pressure in the chest can hinder the functioning of the heart, major blood vessels, and other organs, potentially leading to death if left untreated. Additionally, spontaneous pneumothorax is a recurring problem with a high risk of recurrence, requiring continued monitoring and further treatment if necessary. Primary spontaneous pneumothorax (PSP) refers to the accumulation of air in the pleural space without any traumatic or iatrogenic cause [1]. The incidence rate of PSP is approximately 18-28/100,000 per year for men and 1.2-6/100,000 per year for women [2]. The most common cause of PSP is the rupture of apical subpleural blebs, and it mainly affects young, tall, and thin men [3]. The treatment of PSP varies significantly, resulting in significant heterogeneity in treatment approaches [4]. The objectives of our study are to identify the predisposing factors in PSP patients, determine which patients should undergo genetic analysis, and present the results of a new treatment algorithm.

## Materials and methods

The study is a retrospective cohort study in which the potential causes of a spontaneously occurring outcome are examined during the study period without any intervention. In this particular study, the outcome under investigation is PSP, and its possible causes were explored during the study period. The study sample comprises cases of primary spontaneous pneumothorax who sought medical attention at the emergency department between January 2019 and December 2021 and were subsequently admitted to the pediatric surgery clinic. The participants were requested to return to the hospital for the study, and their demographic data, radiological findings, and molecular genetic analyses were conducted to determine the causes of PSP.

Upon admission to the emergency department, chest X-rays were obtained in all cases following initial medical history and examinations. In appropriate cases, thorax computed tomography (CT) was also performed. Once pneumothorax was diagnosed, follow-up or intervention decisions were made based on the extent of lung atelectasis. Treatment planning was subsequently carried out with thorax CT or high-resolution computed tomography (HRCT) after the acute phase. The clinical protocol utilized in the treatment of the cases is outlined below.

1. If the distance between the lung and chest wall is less than 1 cm (in the form of a collapse) and there is no respiratory distress, only serial chest X-rays and/or thorax CT/HRCT are performed, and the patient is followed up in the service or intensive care unit.
2. If the distance is between 1-2 cm, needle aspiration under ultrasound guidance is performed, and the patient is followed up in the intensive care unit with serial chest X-rays and CT/HRCT.

3. If the distance is larger than 2 cm, sedation is applied, and tube thoracostomy (TT) is performed under surgical conditions, and the patient is followed up with serial chest X-rays and CT/HRCT, and intensive care unit monitoring is performed for air leakage- oscillation.

4. Autologous blood patch application in cases where air leakage continues (repeated twice if necessary).

5. Segmentectomy and pleurodesis with video-assisted thoracoscopic surgery (VATS) in cases where air leakage continues.

6. Segmentectomy and pleurodesis with thoracotomy in cases where air leakage continues.

Participants who were discharged after successful treatment were invited for a follow-up examination during the study period, and their demographic characteristics were documented. In addition, genetic analysis was requested from the participants to assess the presence of syndromes commonly associated with PSP. Fourteen patients were invited for a follow-up examination, but three of them declined to undergo genetic testing. The remaining 11 patients underwent genetic analysis.

**Radiological assessment:** The initial evaluation was performed by the surgeon, who subsequently made necessary treatment and follow-up decisions. An anteroposterior chest X-ray obtained upon admission to the hospital was sufficient to determine whether follow-up or TT was required. Thorax CT or high-resolution thorax CT (HRCT) was used to identify lesions and plan possible interventions once respiratory distress and lung expansion had subsided. A single radiologist evaluated chest radiographs, CT, and/or HRCT images of all patients under elective conditions. The primary pathological findings observed included air cysts (blebs), pleural thickening, and fibrotic changes. The thorax CT slices were 1 cm, and the HRCT slices were 2 mm (with 0.8 mm spacing).

**Genetic analysis:** Genetic analysis was requested from patients on a voluntary basis to identify possible gene mutations and syndromes. Eleven patients agreed to the genetic analysis request.

**DNA isolation:** 200 µl of peripheral venous blood sample collected in an EDTA tube was taken from all patients included in this study. DNA isolations from peripheral blood were performed according to the standard procedure of the High Pure PCR Template Preparation Kit (Roche, Germany). DNA concentrations were measured using Qubit 3.0 (Invitrogen dsDNA HS Assay Kit).

Permissions were obtained from the participating families and institution for this study, and approval was granted by the Balikesir University Faculty of Medicine Clinical Research Ethics Committee (2021/259). Traumatic and iatrogenic pneumothorax cases were excluded from the study.

### Statistical analysis

Statistical analyses were performed using MedCalc for Windows, version 19.1 (MedCalc Software). A normal distribution of the data was verified using the Kolmogorov-Smirnov test. The homogeneity of variance was determined using the Levene test. The level of statistical significance was set at *P*-value less than 0.05.

## Results

Between January 2019 and December 2021, 14 patients were treated for PSP. Ten of the patients were male, and four were female. The average age of the patients was 16.14 (0.95) years. PSP was detected on the right side in nine male patients and on the left side in one male patient, while in females, it was detected on the right side in two patients and on the left side in another two patients.

The complaints that brought the patients to the emergency room were difficulty breathing and back pain. Five male patients presented to the emergency room with symptoms that had started more than 6 hours prior, while the others presented within 1 hour.

Out of the 14 patients in our cohort, only one recovered with follow-up alone (protocol 1). TT was applied to the remaining 13 patients (protocol 3). All but three of them (patients 11, 13, and 14) were successfully treated. One of the remaining three patients (patient 11) received an autologous blood patch (protocol 4), but despite it being repeated twice, the air leak did not close. Consequently, segmentectomy with VATS (protocol 5) was performed on all three patients.

The mean tube withdrawal time was 3.2 (0.35) days, and the mean body mass index (BMI) of all patients was 20.7. The mean BMI was 20.53 in the patients who underwent protocol 3, while it was 21.03 in those who underwent protocol 5, but the difference was not statistically significant.

Radiological pathology was detected in three of the patients who underwent protocol 3 and in all three patients who underwent protocol 5.

Genetic analysis was performed on 11 of the 14 patients, and the results are shown in Table 1. Among these patients, Folliculin (FLCN) mutation was detected in two individuals (patients 11 and 12), but no similarities were observed in terms of BMI, radiological pathology, or treatment protocol.

Table 1: Patient information

No	Gender	Side	BMI	Radiologic findings	Genetic analysis	Treatment steps
1	M	R	21.4	Normal	NA	1
2	M	R	20.9	Air cysts	NA	3
3	M	R	22.7	Normal	NA	3
4	F	L	19.8	Normal	Normal	3
5	M	R	21.6	Air cysts	Normal	3
6	M	R	20.4	Normal	Normal	3
7	M	R	19.6	Normal	Normal	3
8	F	R	19.4	Pleural thickening	Normal	3
9	F	L	19.5	Normal	Normal	3
10	M	L	23.1	Air cysts	Normal	3
11	M	R	20.4	Air cysts, Pleural thickening	Mutation +	3-4-5
12	M	R	18.3	Normal	Mutation +	3
13	F	R	19.2	Air cysts, Fibrotic changes	Normal	3-5
14	M	R	23.5	Air cysts, Fibrotic changes	Normal	3-5
<b>Total</b>	4 F 10 M	11 R 3 L	20.7	7 Normal 7 Pathologic	2 Abnormal	

M: Male, F: Female, R: Right, L: Left, BMI: Body Mass Index, NA: Not applicable

## Discussion

Pneumothorax is a condition characterized by the entry of air between the two layers of the pleura. It can develop due to various causes, such as trauma, infection, iatrogenic factors, or idiopathic-spontaneous reasons. The most common symptom of pneumothorax is respiratory distress. Spontaneous pneumothorax

is often observed in adolescent boys, typically on the right side of the thorax.

The guidelines for treating PSP prepared by the British and American Thoracic Societies are designed for adults. According to these guidelines, if the distance between the thoracic wall and the lung tissue is between 2 and 3 cm, the condition is considered serious, and intervention is recommended. However, there are differences in the thorax structure between adults and children, as well as in how the severity of pneumothorax presents clinically in these populations. As a result, the use of these guidelines is limited in pediatric cases. For this reason, our clinic has developed a partially different treatment algorithm [5]. This algorithm suggests that needle aspiration may be the first treatment option if the pneumothorax is below 20% of the thoracic surface area. For patients with a higher percentage of pneumothorax, the application of a chest tube may be sufficient. If neither treatment is successful, further surgical intervention should be considered [6].

High-resolution computed tomography (HRCT) has been described as an excellent technique for studying lung diseases in children. It can be very helpful in confirming the presence and extent of lung disease. When combined with clinical findings, HRCT can suggest an accurate clinical diagnosis and eliminate the need for biopsy [5,7]. It is particularly useful in children with diffuse airways and interstitial lung disease [8,9]. In our series of patients with PSP, air cysts (blebs), pleural thickening, and fibrotic changes are often observed during radiological evaluation. It is important to note that air cysts smaller than 1 cm can be easily detected by taking a 2 mm cross-sectional slice with HRCT. However, cysts smaller than 1 cm (2 mm cross-section - 8 mm gap) that do not enter the cross-sectional area may be overlooked.

Thorax CT involves taking 1 cm sections, which allows for the detection of all lesions in that range but with low resolution. Following CT scans, 3D studies are performed to increase the probability of detecting lesions with sagittal and coronal sections. In our series, no significant superiority was found between thorax CT and HRCT due to these factors.

The stepped treatment protocol was found to make decision-making and planning easier based on the clinical conditions and radiological variables of the patients. Patients 11, 13, and 14 were considered to have advanced-stage PSP due to recurrent complaints and/or continued air leakage. It is unclear whether the radiological findings of fibrotic changes and pleural thickening were due to a previous infection. Based on anamnesis and background information, these patients were diagnosed with PSP since no infection was detected prior to admission. It was observed that the patients had a low BMI and asthenic body structure, leading to the consideration of examining the development of PSP in tall and thin children in terms of a potential syndromic problem.

Pneumothorax can sometimes be a symptom of a multisystem genetic syndrome, which can be divided into three classes: 1) those caused by mutations in tumor suppressor genes, 2) connective tissue disorders, and 3) syndromes in which the normal lung architecture is deleted [1,10]. Studies have found that mutations in the FLCN gene can cause pneumothorax in

children, resulting in either a single event or recurrent attacks [9]. To detect possible genetic causes of pneumothorax, thoracic CT and genetic testing are recommended [1,9]. Although the function of the FLCN gene is not yet known, studies in mice have demonstrated that it regulates the mammalian target of Rapamycin (mTOR) pathway [1]. In Birt-Hogg-Dubé syndrome (BHD), which is characterized by skin fibrofolliculomas, multiple lung cysts, spontaneous pneumothorax, and kidney cancer, mutations in the FLCN gene have been detected. FLCN is located on chromosome 17p11.2 and contains 14 exons that encode folliculin, an evolutionarily conserved protein consisting of 579 amino acids with no significant homology to any other human protein [8]. In BHD, the incidence of PSP is high, and the risk of kidney cancer is seven times higher [8,9]. The European BHD consortium has reported that patients with PSP and FLCN mutations have a high risk of renal malignancy, regardless of familial phenotype [7].

### Limitations

The severity of complaints in PSP cases may differ when radiological and genetic results are evaluated together. Radiological pathology may not be revealed in every patient, and the probability of detecting a genetic abnormality is uncertain. Although our series had a limited number of patients, genetic mutations were not found to be significant in children with PSP. While providing genetic counseling to these children and their families to detect syndromic problems is important, genetic analysis cannot be recommended for all PSP cases based on our current knowledge.

### Conclusions

It should be noted that PSP may develop in cases with low BMI values and FLCN mutations detected for another reason. Since classical treatment protocols are insufficient in children, the stratified treatment protocol is guided by radiological findings. The creation of prospective series will shed light on the future of PSP treatment in children.

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