Autosomal Recessively Inherited Familial Primary Spontaneous Pneumothorax: A Large Family with Frequent Consanguineous Marriages

Otozomal Resesif Olarak Aktarılan Ailesel Primer Spontan Pnömotoraks: Sık Akraba Evlilikleri Yapmış Geniş Bir Aile

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ABSTRACT Objective: The objective of this study is to determine the clinical and hereditary characteristics of Familial Primary Spontaneous Pneumothorax (FPSP) observed in a number of individuals within a large family. **Material and Methods:** In the medical history of the patient, who applied to the Emergency Department due to a severe difficulty in breathing and was diagnosed with a bilateral Primary Spontaneous Pneumothorax (PSP) and received a bilateral tube thoracostomy performed by the pediatric surgery clinic, it was determined that there were 8 individuals in his family circle who had been affected by PSP disease. All the demographic, clinical, laboratory, radiological, and hereditary data of these individuals were collected. **Results:** In the physical examination of the patients, there were incisional scars of tube thoracostomy and/or thoracoscopy and/or thoracotomy over the rib cages of 6 cases. While the other system examinations and laboratory findings were normal of all patients, seven of the cases have radiological changes at low- and mid- levels - in the lungs in the thoracic computerized tomography. Based on the drawn family tree, we suggest that the FPSP in this family occurred through autosomal recessive heredity. **Conclusion:** We believe that the PSP seen in this family is familial and transferred through autosomal recessive inheritance and the common consanguineous marriages within the family plays a role in the intensity of the disease. Further research on molecular level is required in order to better understand the precise genetic reasons that are lying under the developed FPSP disease of these eight patients.

Key Words: Pneumothorax; genetic predisposition to disease

ÖZET Amaç: Bu çalışmanın amacı sık akraba evliliklerinin mevcut olduğu geniş bir ailede fazla sayıda bireyde gözlemlenen ailesel primer spontan pnömotoraks'ın (FPSP) klinik ve kalıtımsal özelliklerini saptamaktır. **Gereç ve Yöntemler:** İleri derecede solunum sıkıntısı nedeniyle acil servise müracaat eden ve çocuk cerrahi kliniği tarafından bilateral primer spontan pnömotoraks (PSP) tanısı konarak bilateral tüp torakostomi uygulanan bir bireyin (İndex hasta) anamnez'inde ailesinde, PSP hastalığından etkilenen 8 bireyin mevcut olduğu saptandı. PSP'den etkilenmiş oldukları belirlenen bu bireylerin tüm demografik, klinik, laboratuvar, radyolojik ve kalıtımla ilgili verileri toplandı. **Bulgular:** Hastaların fizik muayesinde, 6 olguda sağ veya sol göğüs kafesi üzerinde tüp torakostomi ve/veya torakoskopi ve/veya torakotomi insizyon skarları mevcuttu. Diğer sistem muayeneleri ve laboatuvar bulguları normal iken, 7 olguda göğüs bilgisayarlı tomografide, akciğerlerde hafif ve orta düzeyde patolojik değişiklikler saptandı. Çizilen aile ağacına dayanarak bu ailedeki FPSP'ın otozomal resesif kalıtım ile geçtiğini öne sürebiliriz. **Sonuç:** Söz konusu bu ailede görülen PSP'ın ailesel olduğu, otozomal resesif olarak aktarıldığı ve ailedeki yaygın akraba evliliklerinin hastalığın yoğunlaşmasında rol oynadığını düşünmekteyiz. Sekiz FPSP gelişen bu ailedeki kesin genetik nedenin ne olduğunun anlaşılması için ileri moleküler düzeyde araştırmalara ihtiyaç duyulmaktadır.

Anahtar Kelimeler: Pnömotoraks; hastalığa genetik yatkınlık

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Primary Spontaneous Pneumothorax (PSP) is a kind of a pneumothorax that occurs in the pleural space without a triggering cause like a trauma or a lung disease.[1] PSP is generally sporadic. Risk factors of PSP include being male, being tall, smoking, and family history (genetic background). On the other hand, Familial Primary Spontaneous Pneumothorax (FPSP) is rarely observed.[2] FPSP could be one of the manifestations of Ehlers Danlos Syndrome, Marfan Syndrome, and other connective tissue disorders.[3,4] The genetic and molecular basis of FPSP is still not clearly understood.[5] There is not only genetic but also clinical heterogeneity in FPSP.[6-8] The clinical picture of the disease may come to light through the combinations of different organ and system involvements.[8] Although Koivisto and Mustonen reported that the autosomal recessive inheritance was responsible for the 2 cases with FPSP, most researchers hold the idea that the autosomal dominant inheritance responsible for FPSP.[9] In a minority of cases there is a recessive transition due to X-linked. Even though the male gender is dominantly affected by FPSP, it can still be seen in both genders.[6,7,10,11]

The aim of this study was to investigate the demographic, clinical, laboratory, radiological and hereditary characteristics of 8 PSP cases within an extended family in which frequent consanguineous marriages are seen.

MATERIAL AND METHODS

A 16-year-old male patient (index patient) applied to the emergency department with the complaint of a sudden onset of dyspnoea (difficulty in breathing) and bilateral chest pain. During radiological examination, a bilateral pneumothorax was determined, and an urgent bilateral thoracostomy was performed to the patient at the pediatric surgery clinic (Figure 1). In his family's medical history, it was stated that 7 of his relatives have also developed the same disease. The demographic, clinical, laboratory, and radiological features of the patients was recorded and then the patient was discharged from the hospital after the removal of his left and then his right thorax tubes.

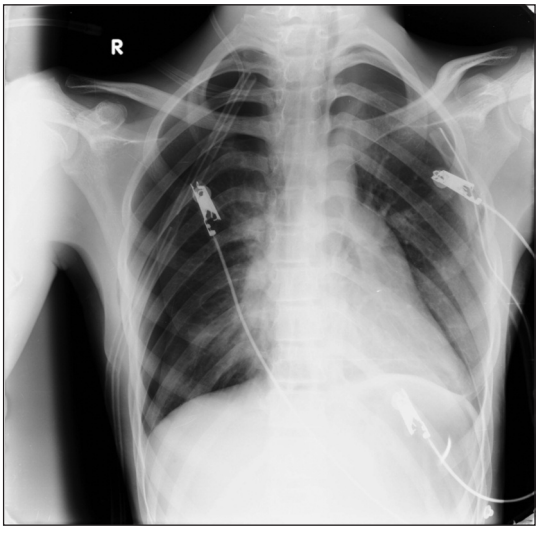

FIGURE 1: X-Ray graphy of the index patient showing bilateral pneumothorax.

This study was confirmed by Ethics Committee of the Medical Faculty of the Fırat University, Elazığ-Turkey. Date and number of the Ethics Committee approval is following: 11.08.2015 and 2015-22, respectively. The study was performed as proper with declaration of Helsinki. The diseased individuals were reached through the information obtained from the index case, and their admission to the hospital were ensured. The demographic data and their family history as well as medical history of the patients (at what age they had this disease; whether they had been exposed to trauma or iatrogenic intervention or not; whether the disease had recurred or not; the diagnosis methods performed; what treatments had been applied; the diseases in regard to the musculoskeletal system and joint-connective tissue disorders experienced either in the past or at present; whether or not they had any symptoms or complaints about pulmonary, liver and renal diseases; their occupational activities and hobbies as well as their smoking habits along with alcohol addiction and medication use) were recorded. By scanning the hospital record system, only one patient's radiological data have been accessed. The patients, whose physical examinations were performed systemically, were evaluated particularly in terms of the skeletal and connective tissue disorders as well as liver, renal, and parenchymal lung diseases such as chronic ob-

structive pulmonary disease, bullous emphysema, interstitial lung diseases, bronchiectasis, tuberculosis, and bronchial asthma. An high resolution computed tomography (HRCT) for the lungs and an abdominal computerized tomography (CT) were obtained to evaluate the liver and the kidneys. Respiratory function tests were performed to evaluate the functions of the lungs according to American Thoracic Society (ATS), and biochemical analysis were performed to evaluate the functions of the liver and the kidneys along with the hematological parameters.[12] Finally, a family tree was formed (genealogical research) by interviewing the elderly individuals within the family (Figure 2).

Descriptive statistics was performed using the computer software statistical package for social sciences (SPSS) for Windows version (16.0).

RESULTS

The demographic, and clinical features of the patients are presented in Table 1. No patients had been exposed to trauma or iatrogenic intervention. Diffuse parenchimal lung diseases were not detected by HRCT. The radiological features of the patients are presented in Table 2. During the physical examinations of the patients, incisional scars on the right or left side of the rib cages of 6 cases due to tube thoracostomy and/or thoracoscopy and/or thoracotomy were observed. The examination of the respiratory and other systems were evaluated as natural. The respiratory function tests of the cases were within normal boundaries according to ATS. In addition, the hematological examinations and biochemical parameters were also within normal boundaries. As it can be seen in Figure 2, the genetic transition within the family is in compliance with the autosomal recessive inheritance pattern.

DISCUSSION

The obtained data suggest that the PSP observed in the individuals of our study group was familial, and that the autosomal recessive inheritance was likely to have been responsible for this transition. The autosomal recessive transition we have suggested for FPSP in this family with frequent consanguineous marriages is in compliance with the findings of Koivisto and Mustonen.[9] In a study, which was conducted by Koivista and Mustenon in 2001, the researchers observed PSP in a sister and a brother of Finnish origin and suggested that this transition was through the autosomal recessive inheritance. Similarly, in this family we studied, the disease leap that was observed among generations and frequent consanguineous marriages are important factors that support the autosomal recessive inheritance.

Although it has been stated in all of the studies conducted so far regarding the heredity of FPSP that women have been affected by FPSP, but surprisingly no female case was found within our study group.[6-11,13] This can be explained as follows: It was reported by the individuals in this family while their family tree (genealogical research) was being formed that the women in this family circle

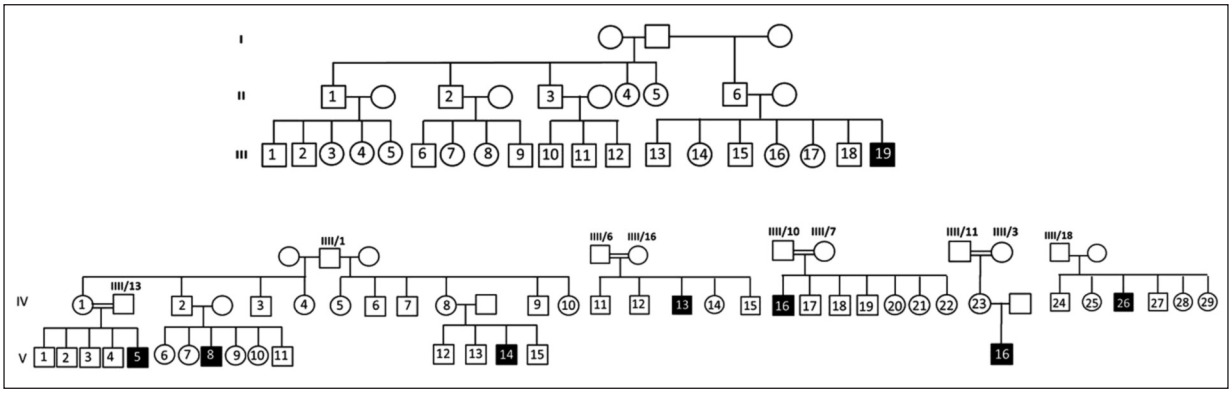

FIGURE 2: Five generation pedigree showing affected members (black) and relatives.

TABLE 1: The demographic and clinic data of the patients.

Variables	Patients								
	III/19	IV/13	IV/26	IV/16	V/5	V/14	V/16	V/8	Mean
Age (years)	46	30	31	29	32	22	16	38	30.50
Age of first episode of pneumotorax (years)	18	27	29	25	22	17	16	20	21.75
Body Mass Index (kg/m^2)	22.40	21.60	20	21.70	23.50	18.60	15.50	24.60	
Body type	Athletic	Athletic	Asthenic	Athletic	Athletic	Asthenic	Asthenic	Athletic	-
Recurrence	Have	Have	No	No	No	Have	Have	No	-
Smoking[1]	1 package/day, 3 years	1 package/day, 7 years	1 package/day, 9 years	1 package/day, 5 years	1 package/day, 3 yıl	Not use	Not use	1 package/day, 2 years	0.75 package/day, 3,60 years
Smoking[2]	1 packet/ day, 28 years	1/4 package/day, 3 years	1 package/day, 2 years	Not use	1/4 package/day, 10 years	Not use	Not use	1/2 package/day, 18 years	0.37 package/day, 7,62 years

[1]: Smoking period until the first episode of pneumothorax

[2]: Smoking period from the first episode of pneumothorax to present time.

had suffered from a number of miscarriages. However, no precise information could be received about genders of the infants that were lost through the spontaneous abortions. It is considered that a number of female infants could have been lost through the spontaneous abortions; therefore, no female individual who was affected by FPSP has been incorporated to the study.

Both the sporadic PSP cases and FPSP-developed cases are usually tall and slim male individuals with asthenic body structures.[9,14] Whereas 5 of the cases incorporated into our study group were athletic, only 3 of them had the appearance of with classic PSP with their asthenic body structures. Six of our cases are still smokers or were smokers in the past, during the PSP disease since they were at a young age or they had smoked for a short period of time, it is clear that there is no underlying smoking related disease, such as chronic obstructive pulmonary disease and bullous emphysema due to smoking (Table 1). Respiratory function tests of all the patients was proved to be normal. Diffuse parenchimal lung diseases such as interstitial lung diseases, bronchiectasis, tuberculosis, and common bullous involvement were not detected in the pulmonary parenchyma of any of our patients in the process of HRCT, except for one case (Table 2).

We are of the opinion that secondary pathological changes may have developed in the patient in question who has kept on smoking for 28 years since the time of that PSP attack. Additionally, changes that are emphysema-like or mild bronchiectatic were identified in 6 cases. These gives rise to the thought that they paved the way for the pathological basis of FPSP (Table 2). Pathomorphological findings in the pulmonary parenchyma of 6 cases are seemed to be in concordance with the findings of Inderbitzi et al. and Cardillo et al.[15,16] The researchers identified pathomorphological changes in the pulmonary parenchyma of more than 94% of the cases with PSP.

On the other hand, when the publications related to FPSP are chronologically reviewed starting from early 2000s (the period when HRCT used to be applied in pulmonary imaging), it can be seen in all the conducted studies that common bullous lesions had been identified in the pulmonary parenchyma of the cases with FPSP. Also, renal and skin pathologies in Birt-Hogg-Dubé Syndrome are accompanied by FPSP, while connective tissue disorders in Ehlers-Danlos and Marfan syndrome are accompanied by FPSP. For all of these reasons, within this large family circle where quite frequent consanguineous marriages occur, the gender rate of the individuals with

TABLE 2: Radiological features and treatments administered to the patients.

Variables	Patients							
	III-19	IV-13	IV-26	IV-16	V-5	V-14	V-16	V-8
Radiological Findings (HRCT)	Common bullous lesions in the both lungs	Centrilobular emphysema tous changes in the upper lobes and tubular bronchiectatic changes in lower lobes of both lungs	Paraseptal emphysematous changes in both lungs	Reticular pattern in both lungs	Normal	Bronchiectatic changes in both lungs	Cicatricial emphysema area in the posterior segment of upper lobe of right lung	Paraseptal emphysematous changes in the apex of each lung
The treatment applied to the first episode and/or recurrences	Right Tube thoracostomy	Right Tube thoracostomy + Surgery	Left Tube thoracostomy	Right Tube thoracostomy	Observation (Right pneumothorax	Left Tube thoracostomy + Surgery	Bilateral Tube thoracostomy + Surgery	Observation (Left pneumothorax)

FPSP, pulmonary radiological findings, and physical characteristics have been determined to be different from what is mentioned in the literature and suggest to the development of FPSP in this family could take place through different physiopathological and/or molecular mechanisms.

The molecular and genetic studies that are conducted recently have revealed that the hereditary mutations found within Folliculine gene (FLCN; MIM 607273), which is located on the short arm of the 17th chromosome (17p11.2), are associated with FPSP.[5,7,8,11] One of the major restrictions of our study is that the molecular genetic analysis of this gene was not performed on our cases with FPSP. Investigating the hereditary mutations in FLCN gene in these cases and their families in prospective studies may contribute to understanding the cause of FPSP that develops within this large family circle that has frequent consanguineous marriages.

In conclusion, in the other publications, it is reported that FPSP accompanied by soft tissue disorders, skin, and renal pathologies while autosomal dominant inheritance is responsible for genetic transition. Therefore, it can stated that our study have different clinical and genetic characteristic from the other publications. Although we have foreseen that the genetic transition of this disease in our case group was the autosomal recessive inheritance, the developed FPSP in 8 people within the same family is considered to be due to frequent consanguineous marriages. In order to better understand what the exact cause of the disease is, which was seen in this family further molecular studies are required.

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