PLEVRAL TÜBERKÜLOZLU HASTALARDA YAŞ VE CİNSİYETE GÖRE PLEVRA SIVISI ADA DÜZEYİNİN KARŞILAŞTIRILMASI

COMPARISON OF PLEURAL FLUID ADA LEVEL IN TERMS OF AGE AND GENDER OF PATIENTS WITH PLEURAL TUBERCULOSIS

Sami DENİZ (0000-0002-8328-295X), **Ahmet Emin ERBAYCU** (0000-0001-6618-6774), **Mutlu Onur GÜÇSAV** (0000-0003-2969-4766), **Dursun ALİZOROĞLU** (0000-0002-6285-3549), **Gülru POLAT** (0000-0002-2211-1268), **Mustafa Şevket DERELİ** (0000-0003-0759-8773)

Sağlık Bilimleri Üniversitesi İzmir Dr Suat Seren Göğüs Hastalıkları ve Cerrahisi Eğitim ve Araştırma Hastanesi, Gögüs Hastalıkları, Izmir, Türkiye

Anahtar sözcükler: Tüberküloz; adenozin deaminaz; yaş; cinsiyet

Keywords: Tuberculosis; adenosine deaminase; age; gender

Geliş tarihi: 10 / 10 / 2018 Kabul tarihi: 05 / 07 / 2019

ÖZ

***Amaç**: Tanı ve tedavideki gelişmelere rağmen, tüberküloz (TB) ülkemizde olduğu gibi tüm dünyada da önemli bir mortalite ve mortalite nedenidir. Çalışmamızda; TB plörezi bulunan hastalarda plevral sıvı ADA düzeyinin yaş ve cinsiyet ile ilişkisinin belirlenmesi amaçlandı.*

***Yöntem ve Gereç**: Çalışma retrospektif bir çalışma olarak tasarlanmıştır. Hastaların yaşı, solunum fonksiyon testleri (SFT), periferik kanda; glikoz, protein, albümin, aspartat aminotransferaz (AST), alanin aminotransferaz (ALT), alkalen fosfataz (ALP), laktat dehidrojenaz (LDH), bilirubin, üre, kreatinin ve kan hücre sayımı; kan gazı analizi, plevral sıvıda; glukoz, albümin, protein, LDH, adenosin deaminaz (ADA) ve sıvı hücre sayımı sonuçları kaydedildi.*

***Bulgular**: Çalışmaya toplam 41'i kadın, 105'i erkek 145 hasta dahil edildi,. Hastaların yaş ortalaması 53.1, ortalama plevral sıvı ADA düzeyi 55.2 idi. Cinsiyete açısından karşılaştırıldığında; plevral sıvı ADA düzeyleri kadınlarda anlamlı olarak düşüktü (p = 0.031). Hastalar 65 yaşından küçük ve büyük olarak ayrıldığında, plevral sıvı ADA düzeyi arasında fark yoktu (p = 0.657).*

ABSTRACT

***Aim:** Despite improvements in the diagnosis and treatment, tuberculosis (TB) is still an important cause of morbidity and mortality all over the world, as it is in our country. **Aim**: It was aimed to determine the relation of pleural fluid adenosine deaminase (ADA) level with age and gender of patients with TB pleurisy.*

***Material andMethods**: The study was designed as a retrospective study. Age of the patients, pulmonary function tests (PFT) measurements, glucose, protein, albumin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), lactate dehydrogenase (LDH), bilirubin, urea, creatinine and blood cell count from peripheral blood; blood gas analysis, glucose, albumin, protein, LDH, ADA, fluid cell count results in pleural fluid were recorded.*

***Results**: A total of 145 patients were included in the study, 41 were female and 105 were male. The mean age of the patients was 53.1 years, the mean pleural fluid ADA level was 55.2. When compared to gender; pleural fluid ADA levels were significantly lower in women (p = 0.031). When patients were divided as younger and older than*

***Sonuç**: Tüberküloz plevral efüzyonlarda adenosin deaminaz düzeyi cinsiyete göre değişmekte ve kadınlarda erkeklere göre daha düşük olduğu saptanmıştır. 65 yaş altı ve üstü gruplar arasında benzer seviyelerde bulunmuştur.*

*65 years old, there was no difference in pleural fluid ADA level (p = 0.657). **Conclusion**: The level of adenosine deaminase in tuberculous pleural effusions varies according to gender and was detected lower in females than in males. Similar levels were found between the groups above and under 65 years old.*

INTRODUCTION

Despite improvements in the diagnosis and treatment, tuberculosis (TB) is still an important cause of morbidity and mortality all over the world, as it is in our country. According to data reported in the 2013 report; pulmonary involvement was found in 59% of 15.679 TB patients, extrapulmonary involvement in 7%, and both lung and extrapulmonary involvement in 4%. The involvement of pleura (31%) and extrathoracic lymph node (30%) were the most commonly reported extrapulmonary TB forms. Where the incidence of pleural TB is high, the cause of pleurisy is also TB (1,2).

A definite diagnosis of TB pleurisy is based on the identification of M. *tuberculosis* from the pleural fluid, sputum and pleural tissue or caseous granulomas in pleural tissue specimens. The direct microscopic positivity rate of the pleural fluid is as low as 3-8% and the culture sensitivity is between 12-70%. Direct microscopic examination of the pleural biopsy can detect 30% of the bacilli and 88% of the *M. tuberculosis* can be isolated in the culture (3-5). Cells that proliferate rapidly in tissues are known to contain higher adenosine deaminase (ADA) activity than non-dividing cells. ADA activity has been used for the diagnosis of TB pleuritis since 1978. It is regarded as a sign of activation, proliferation and differentiation of mononuclear cells (especially T lymphocytes). Tuberculosis is an infectious disease in which cellular immunity is active and the antigen is present in the field where lymphocytes and macrophages activate. The ADA and ADA-2 isoenzyme are high in body fluid samples of TB patients (6,7).

Current studies indicate that ADA is a valuable biochemical parameter in the diagnosis of TB pleurisy. The sensitivity of increased pleural ADA in TB pleuritis varies between 47-100% and specificity is 50-100% (8,9).

In our study; it was aimed to determine the relation of pleural fluid ADA level with age in patients with TB pleurisy.

MATERIALS AND METHODS

Patients who had been followed up for the last 5 years and who were diagnosed as TB pleurisy were examined. The patient's data was obtained from the hospital information management system. 145 patients were included in the study with inclusion criteria from a total of 223 patients with pleural effusion. Age of the patients, glucose, protein, albumin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), lactate dehydrogenase (LDH), bilirubin, urea, creatinine and blood cell count from peripheral blood; blood gas analysis, glucose, albumin, protein, LDH, ADA, fluid cell count results were recorded from the pleural fluid obtained by thoracentesis. Using the new age classification of the World Health Organization, patients were divided and studied for groups older and younger than 65 years. The study was designed as a retrospective case series and approved by the ethics committee.

Inclusion Criteria; TB pleurisy was diagnosed by histopathologically and / or microbiologically and all patients with complete results.

Exclusion Criteria; Patients diagnosed with chronic inflammatory and / or autoimmune disease (COPD, ulcerative colitis, Crohn's disease, rheumatoid arthritis, etc.), cancer or

radiological lung cancer in addition to TB pleurisy diagnosis.

Statistical analysis: The data obtained in the study were entered into the SPSS 18 program, all analyses were performed with the same program. It was accepted that normal distribution with continuous variables and subgroups did not fit with sample size and normal distribution tests. Mann Whitney U test (non-parametric) was used to compare these variables. For all statistical methods, the type 1 error coefficient was determined as alpha = 0.05. In cases where the p-value was less than 0.05, the difference between the groups was considered statistically significant.

RESULTS

A total of 145 patients were included in the study, 41 were female and 105 were male. The mean age of the patients was 53.1 years, mean pleural fluid ADA level was 55.2 (Table 1). A total of 9 patients had the additional disease. 4 patients had diabetes mellitus (DM), 5 patients had hypertension (HT). When the measurements in patients were compared according to gender; pleural fluid ADA levels were significantly lower in women (p=0.031). In contrast; no difference was determined in terms of ADA (>45, ≤45).Blood leukocyte, hemoglobin, hematocrit, ALT, AST, creatinine levels were also statistically significantly lower in women (Table 2).

Table 1. Age, Spirometry, Blood and Pleural Fluid Laboratory Measurements of Patients With Tuberculous Pleural Effusion.

Variables	Mean±SD	Median (Min-Max)
Age (Years)	53,1±22.1	61 (14-90)
pH (fluid)	7,3±0.1	7,33 (3.10-7,51)
Glucose (fluid) (mg/dl)	87±47.5	84 (1-377)
Protein (fluid) (gr/dl)	5±0.9	5,1 (1.5-6.7)
Albumine (fluid) (gr/dl)	2,6±0.5	2,8 (0.6-3.8)
LDH (fluid) (U/L)	801±1029	574 (51-9500)
Adenozin deaminase(fluid)	55,2±29.2	51 (6-216)
Glucose (blood) (mg/dl)	107,7±48.2	98 (8.4-470)
Protein (blood) (gr/dl)	7,1±0.8	7,2 (4.8-8.7)
LDH (blood) (U/L)	218,9±101	200 (124-814)
Albumine (blood) (gr/dl)	3,46	3,5 (2.2-4.8)
Leucocyte (blood) (/mm3)	8,1±1.2	7,6 (3.3-29.6)
Lymphocyte (blood) (/mm3)	1,5±1.1	1,34 (0.2-8.2)
Hemoglobine (blood) (gr/dl)	12,3±1.7	12,3 (8.6-19.8)
Hematocrite (blood) (%)	37,2±4.6	37,6 (26.1-48.7)
Bilirubine (blood) (mg/dl)	0,5±0.2	0,48 (0.1-2.2)
ALT (blood) (U/L)	31,3±32.3	19 (3-223)
AST (blood) (U/L)	39,4±87.6	25 (9-1044)
Urea (blood) (mg/dl)	35,7±22.1	29 (3.8-156)
Creatinine (blood) (mg/dl)	1±0.9	0,9 (0.4-9.5)
Protein (fluid/blood)	0,7±0.1	0,7 (0.2-0.9)
LDH (fluid/blood)	4±4.7	2,8 (0.2-28.6)
Albumine (fluid/blood)	0,7±0.1	0,7 (0.2-1.6)
Albumine (fluid/blood)	0,7±0.5	0,8 (-1.3-2.6)
Protein (blood-fluid)	2±0.8	2 (0.3-4.8)

LDH: Lactate dehidrogenase, ALT: alanine aminotransferase, AST: aspartate aminotransferase

Table 2. General and Blood / Pleural Fluid Laboratory Measurements of Patients According to Gender.

	Female (n=41, %28)		Male(n=104, %72)		
Variables	Mean±SD	Med (Min-Max)	Mean±SD	Med (Min-Max)	P value
Age (Years)	53±25.24	61 (15-90)	53,2±20.9	61 (14-86)	0,685
pH (fluid)	7,3±0.1	7,36 (6.93-7.49)	7,29±0.18	7,33 (6.10-7.51)	0,007
Glucose (fluid) (mg/dl)	93,7±62.9	82,5 (1-377)	84,4±40.1	85 (1-297)	0,636
Protein (fluid) (gr/dl)	5±0.9	5,25 (2.1-6.6)	5,05±0.9	5,1 (1.5-6.7)	0,799
Albumine (fluid) (gr/dl)	2,6±0.6	2,8 (1.1-3.4)	2,6±0.5	2,7 (0.6-3.8)	0,717
LDH (fluid) (U/L)	684±749	493 (51-3546)	845±1116	584 (116-9500)	0,077
Adenozin deaminase (fluid)	46±22.3	49 (6-95)	58,8±30.8	52,5 (9-216)	*0,031*
Glucose (blood) (mg/dl)	116,8±49.3	100 (59-275)	104,1±47.6	98 (8.4-470)	0,379
Protein (blood) (gr/dl)	7,1±0.8	7,25 (5.4-8.7)	7,1±0.8	7,1 (4.8-8.7)	0,606
LDH (blood) (U/L)	205±52	206 (124-296)	225±116	196 (129-814)	0,977
Albumine (blood) (gr/dl)	3,5±0.5	3,6 (2.2-4.3)	3,4±0.5	3,4 (2.2-4.8)	0,182
Leucocyte (blood) (/mm3)	6,8±1.7	6,8 (3.3-10.1)	8,6±3.7	8 (3.6-29.6)	*0,002*
Lymphocyte (blood) (/mm3)	1,2±0.4	1,32 (0.2-2.4)	1,5±1.2	1,3 (0.3-8.2)	0,361
Hemoglobine (blood) (gr/dl)	11,5±1.2	11,6 (8.8-13.5)	12,6±1.7	12,9 (8.6-19.8)	*0*
Heamotocrite (blood) (%)	35,1±3.5	35,4 (27.7-44.3)	38,1±4.7	38,5 (26.1-48.7)	*0*
Biluribine (blood) (mg/dl)	0,48±0.2	0,45 (0.1-1)	0,5±0.3	0,48 (0.1-2.2)	0,751
ALT (blood) (U/L)	19,1±14.6	15 (3-75)	36,1±36	24 (4-223)	*0,001*
AST (blood) (U/L)	27,5±19.6	21 (12-92)	44±102	26 (9-1044)	*0,036*
Urea (blood) (mg/dl)	32±19.1	28,5 (12-91)	37,2±23.1	29 (3.8-156)	0,103
Creatinine (blood) (mg/dl)	0,8±0.2	0,8 (0.48-1.42)	1,1±1.1	0,9 (0.5-9.5)	*0*
Protein (fluid/blood)	0,7±0.1	0,7 (0.33-0.93)	0,7±0.1	0,7(0.2-0.9)	0,161
LDH (fluid/blood)	5±8	2,2 (0.28-28.6)	3,6±2.4	3,1(0.1-9.8)	0,414
Albumine (fluid/blood)	0,7±0.1	0,79 (0.3-1)	0,7±0.1	0,7 (0.2-1.6)	0,717
Albumine (blood-fluid)	0,8±0.4	0,8 (-0.1-2.6)	0,7±0.5	0,8 (-1.3-2.5)	0,749
Protein (blood-fluid)	2±0.9	1,8 (0.4-4.8)	2±0.7	2 (0.3-4.4)	0,434

LDH: Lactate dehidrogenase, ALT: alanine aminotransferase, AST: aspartate aminotransferase

When patients were divided as younger and older than 65 years old, there was no difference in pleural fluid ADA level (p=0.657). When categorized into three groups according to age (<18, 18-64, ≥65), it was not detected significance in terms of ADA (>45, ≤45) (p=0.512). In the group below 65 years; bilirubin and urea in the blood, glucose in the blood and pleural fluid were significantly lower. In the group below 65 years; protein and albümin in the blood and pleural fluid, LDH, lymphocytes, hemoglobin, hematocrite in the blood were higher (Table 3).

DISCUSSION

Tuberculous pleurisy is one of the most common involvement of extrapulmonary tuberculosis. Analysis of pleural fluid and closed pleural biopsy are required for diagnosis. Adenosine deaminase is a purine metabolism enzyme. It is the most cost-effective screening test routinely used in the world, especially in endemic countries (10,11). Several ADA cut-off values ranging from 30-100 IU/L (international unit / liter) were used in several studies that reported different sensitivity and specificity. This difference; it is thought that the use of different measurement methods or the TB prevalence in various study populations may even lead to differences in study population characteristics. It has been estimated that the demographic features of the disease may affect the pleural fluid ADA level (12). In a study involving 309 patients

with pleural effusion; there was a significant negative correlation between age and pleural fluid ADA level. In the subgroup of 174 patients with TB pleurisy, it was stated that there was no correlation between age and pleural fluid ADA, and a false negative rate was reduced when a lower level of cut-off value (29 IU/L) determined. If this is taken into account, accurate diagnosis can be obtained in a large number of patients in countries with a high prevalence of TB (13).

Table 3. General and Blood / Pleural Fluid Laboratory Measurements in Patients above/under 65 Years Old

Variables	≤65 (n=81, %55)		>65 (n=64, %45)		
	Mean	Median (Min-Max)	Mean	Median (Min-Max)	P value
Age	37,2±15.9	35 (14-64)	73,3±7.6	70 (65-90)	
pH (Sıvı)	7,3±0.1	7,33 (6.19-7.49)	7,3±0.1	7,34 (6.10-7.51)	0,108
Glucose (fluid) (mg/dl)	75,2±27.6	79 (1-119)	101,8±61.3	89 (1-377)	*0,003*
Protein (fluid) (gr/dl)	5,2±0.7	5,3 (2-6.7)	4,7±1.1	4,9 (1.5-6.6)	*0,002*
Albumine (fluid) (gr/dl)	2,8±0.4	2,9 (0.6-3.8)	2,4±0.5	2,6 (0.7-3.6)	*0*
LDH (fluid) (U/L)	735±608	577 (116-5060)	885±1393	570 (51-9500)	0,22
Adenozin deaminase (fluid)	56,4±28.3	51 (9-192)	53,6±30.3	51,5 (6-216)	0,657
Glucose (blood) (mg/dl)	95,5±22.7	94 (16-179)	124±66	107 (8-470)	*0,001*
Protein (blood) (gr/dl)	7,2±0.7	7,3 (4.8-8.7)	6,9±0.8	6,8 (4.9-8.7)	*0,005*
LDH (blood) (U/L)	220±77	214 (126-653)	215±131	175 (124-814)	*0,036*
Albumine (blood) (gr/dl)	3,6±0.5	3,7 (2.2-4.8)	3,2±0.4	3,3 (2.2-4.4)	*0*
Leucocyte (blood) (/mm3)	7,7±2	7,7 (3.6-13.7)	8,5±4.5	7,35 (3.3-29)	0,814
Lymphocyte (blood) (/mm3)	1,6±0.6	1,5 (0.4-4.7)	1,3±1.5	1,1 (0.2-8.2)	*0*
Hemoglobine (blood) (gr/dl)	12,7±1.7	12,6 (8.6-19.8)	11,8±1.5	12,1 (9-14,9)	*0,002*
Hematocrite (blood) (%)	38,4±4.4	38,5 (26.1-48.7)	35,8±4.5	35,6 (26.8-45.8)	*0,001*
Biluribine (blood) (mg/dl)	0,4±0.2	0,4 (0.1-2.2)	0,5±0.2	0,52 (0.2-1.4)	*0,006*
ALT (blood) (U/L)	32±34	19 (4-223)	29,5±29.1	20 (3-148)	0,605
AST (blood) (U/L)	33±26	24,5 (9-166)	47±128	25,5 (12-1044)	0,775
Urea (blood) (mg/dl)	28,1±17.7	24 (12-156)	45,4±23.4	43 (3.8-124)	*0*
Creatinine (blood) (mg/dl)	1±1.2	0,9 (0.4-9.5)	1,1±0.6	0,9 (0.5-5.3)	0,075
Protein (fluid/blood)	0,7±0,1	0,7 (0.3-0.9)	0,6±0.1	0,7 (0.2-0.9)	0,295
LDH (fluid/blood)	3,5±2.1	2,8 (0.2-9.8)	4,9±7.1	2,5 (0.2-28.6)	0,395
Albumine (fluid/blood)	0,7±0.1	0,7 (0.2-1.6)	0,7±0.2	0,7 (0.2-1.4)	0,827
Albumine (blood-fluid)	0,7±0.4	0,9 (-1.3-1.8)	0,7±0.6	0,7 (-0.9-2.6)	0,231
Protein (blood-fluid)	2±0.7	2 (0.3-4.8)	2,1±0.9	2,1 (0.3-4.4)	0,586

LDH: Lactate dehidrogenase, ALT: alanine aminotransferase, AST: aspartate aminotransferase

The ADA cut-off level for the diagnosis of TB pleurisy in the elderly group is much lower than that of the younger group.The decrease in ADA as age increases is not a constant change in all age groups (12). When we examined tuberculosis pleurisy patients below age 65 and above; there was no difference in pleural fluid ADA levels between these two age groups. When the other laboratory parameters are examined; in the group below 65 years; bilirubin and urea in the blood, glucose in the blood and pleural fluid were significantly lower. In the group below 65 years; protein and albümin in the blood and pleural fluid, LDH, lymphocytes, hemoglobin, hematocrit in the blood were higher.

With its simplicity, low cost and resulting in 24 hours, the ADA test has been successfully used in practice for many years (14).

ADA level above 40 IU/L is very effective in differentiating TB pleuritis from exudative pleural fluids formed by other causes (15,16). Despite the high sensitivity of ADA measurement, diagnostic specificity is affected by the local prevalence of TB, laboratory methodology, population ethnicity, and other clinical conditions (17-19). To diagnose tuberculous pleurisy, pleural fluid ADA level should be interpreted with clinical, radiological and laboratory findings of the patient to exclude non-TB diseases and to increase positive predictive value. In a study of 157 TB pleurisy patients; pleural fluid ADA level is not affected by gender, age or comorbidity. In this study, pleural fluid ADA level supporting TB pleurisy was suggested as 26.5-100 IU/L. Values above 100 IU/L have been stated to exclude TB pleurisy (20). When the pleural fluid ADA level was analysed according to gender in patients with TB pleurisy in our study, ADA was significantly lower in female patients than in males. Besides, blood leukocyte, hemoglobin, hematocrit, ALT, AST, creatinine levels in women were significantly lower than male patients.

Biochemical studies are of limited value in the diagnosis of tuberculous pleurisy. Classically, total protein levels above 5.0 g/dL are expressed as significant for TB pleurisy (21). In our study, the mean total protein level of TB pleurisy cases (5±0.9 gr/dl) was compatible with the literature. Tuberculous pleurisy; parapneumonic effusion, empyema and rheumatoid pleurisy together with low pleural glucose levels are among the most common four diseases. However, it is also known that the pleural glucose level is greater than 60 mg/dL in the majority of patients with TB pleurisy (22). Pleural fluid pH is usually between 7.30 and 7.40, rarely below 7.30 (3). In this study the mean pleural glucose level was 87±47.5 mg/dl and mean pleural fluid pH was 7,30±0.1. Significant changes in pleural fluid biochemical values are thought to be insignificant in clinical practice.

The association of diabetes and TB infection is a well-known condition. Ruan et al. (4)in their study, there was DM at 19% of patients with TB pleurisy, Ak et al. (11)reported that DM was the most common underlying disease with an incidence of 10.3%. In the study of Yarpuzlu et al. (23); five of the patients (9.3%) had DM which was the most common underlying cause. In our study; the incidence of DM was 2% in patients with TB pleurisy (four patients). Pleural effusion in tuberculous pleurisy studies that investigate ADA levels concerning age includes comparative studies in a wide range of age groups. A differentiation and limitation of our study are thought to be the separation of patients into two age groups according to the new World Health Organization age classification and the analysis of over and lower than 65 years of age and retrospective data collection. There is still no ideal diagnostic method for tuberculous pleurisy. By examining pleural specimens together with microbiological and histopathological methods, the diagnostic efficiency ratio is increasing seriously. Also, the fluid biochemical properties of TB pleurisy and ADA levels are important markers that support the diagnosis. In our study, the mean age and pleural glucose levels were higher than expected. Comorbidities were found to be

lower in proportion. The retrospective nature of the study may have contributed to these results and is a restriction for the study.

In conclusion: The level of adenosine deaminase in tuberculous pleural effusions varies according to gender and is lower in females than in males. Similar levels were found between the groups above and under 65 years old.

Compliance with Ethical Standards

Funding: The authors declare no any financial support.

Conflict of Interest: The authors declare no potential conflicts of interest

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Yazışma Adresi:

Dr. Sami DENİZ
Sağlık Bilimleri Üniversitesi İzmir Dr Suat Seren Göğüs Hastalıkları ve Cerrahisi Eğitim ve Araştırma Hastanesi, GogusHastaliklari, Izmir
e-mail: sami_deniz@yahoo.com