NT-PRO BRAIN NATRIURETIC PEPTIDE: NEW DIAGNOSTIC TOOL FOR HEART FAILURE RELATED PLEURAL EFFUSION

NT-PRO BNP NATRİÜRETİK PEPTİT:KALP YETMEZLİĞİNE BAĞLI PLEVRAL EFFÜZYONDA YENİ TANI ARACI

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ÖZET

Amaç: *Transüdatif ve eksüdatif sıvıları özellikle diüretik kullanan kalp yetmezliği olan hastalarda birbirinden ayırt etmek bazen zor olmaktadır. Bu çalışmanın amacı kalp yetmezliğine bağlı plevral effüzyonları kalp yetmezliği olmayan plevral effüzyonlardan ayırmada plevral sıvı NT-pro BNP'nin tanısal değerini araştırmaktır.*

Materyal ve method: *Plevral effüzyonu olan 126 hasta çalışmaya alındı. Plevral sıvı ve serum örnekleri eş zamanlı laboratuvara gönderildi. Biyokimyasal analiz, bakteriyel ve mantar kültürü, mycobacterium tuberculosis için yayma ve kültür ve sitolojik inceleme yapıldı.*

Bulgular: *Kalp yetmezliğine bağlı plevral effüzyonlarda NT-proBNP değeri diğer plevral effüzyon nedenlerine göre istatistiksel olarak yüksek saptandı (p<0,001). Plevral sıvı ve serum NT-proBNP değerleri arasında istatistiksel olarak anlamlı korelasyon saptandı (r: 0.91, p <0.001). Kalp yetmezliğine bağlı plevral effüzyonları kalp yetmezliğine bağlı olmayan plevral effüzyonlardan ayırmada plevral sıvı NT-proBNP cut off değeri 5133 pg/ml'de duyarlık %51,8, özgüllük %98,9 (p:0,000), tanı doğruluğu da %84,1 idi.*

SUMMARY

Aim: *Definite diagnosis of transudative or exudative pleural fluids often presents a diagnostic dilemma. The aim of this study was to evaluate whether amino-terminal pro-brain natriuretic peptide (NT-proBNP) levels in pleural fluid has a diagnostic value for discriminating heart-failure related pleural effusions from non-heart-failure effusions.*

Methods: *One hundred twenty six subjects with pleural effusions were included. Samples of pleural fluid and serum were obtained simultaneously from each subject. Biochemical analysis, bacterial and fungal culture, acid-fast bacilli smear, culture and cytology were performed on the pleural fluid.*

Results: *Subjects with heart-failure-related pleural effusion had significantly higher pleural NT-proBNP levels than other subjects (P < 0.000). Pleural and serum NT-proBNP measures were closely correlated. An NT-proBNP cut off value of > 5133 pg/mL in pleural fluid had a sensitivity of 51.8%, a specificity of 98.9%, respectively (P=0.000, diagnostic accuracy 84.1%) for discriminating transudates caused by heart failure from exudates.*

Sonuç: *Kalp yetmezliği ile ilişkili plevral sıvı düşündüğümüz ve ayrıca özellikle diüretik tedavisi altında olup eksüdatif effüzyonla karşımıza çıkan kalp yetmezliğindeki hastalarda plevral sıvı NT-proBNP değerini tanı aracı olarak kullanmamız yararlı olabilir.*

Conclusions: *Pleural fluid NT-proBNP measurement in the routine diagnostic panel may be useful in differentiation of heart-failure-related pleural effusions and exudative pleural fluids with reasonable accuracy, especially in heart-failure patients treated with diuretics.*

INTRODUCTION

Pleural fluid is classically classified as a transudate or an exudate, which helps in determining the cause of pleural effusions. The criteria of Light et al are used as a first step to differentiate transudates from exudates in the work up of patients with pleural effusion (1). However, these criteria have some limitations, especially in patients with heart failure and taking diuretics (2,3).

Amino-terminal brain natriuretic peptide precursor (NTproBNP) is a member of vasoactive peptides produced from the heart. NT-proBNP measured in serum is a convenient tool for heart failure but little is known about the utility of pleural fluid NT-proBNP.

Therefore we evaluated the diagnostic accuracy of pleural fluid NT-proBNP in differentiation of heart-failure-related pleural effusions from non-heart-failure- related effusions.

MATERIAL AND METHODS

Study population and diagnostic evaluation

126 consecutive subjects with pleural effusions who undergo diagnostic thoracentesis were included prospectively into the study. The demographic and clinical parameters of the subjects were noted. Pleural fluid and serum samples were obtained simultaneously from each subject. Biochemical analysis (including lactate dehydrogenase (LDH), protein, albumin, glucose, blood ureanitrogen, and creatinine), bacterial and fungal culture, acid-fast bacilli smear, polymerase chain reaction test for Mycobacterium tuberculosis, and cytologic examinations were performed on all pleural fluid samples. Further investigations, such as pleural biopsy were performed at the discretion of the primary physicians. Chest x-ray and electrocardiography were obtained from each subject.

NT-proBNP was measured by electrochemiluminescence immunoassay.

Pleural effusions were categorized as either exudates or transudates according to the criteria of Light et al (1). The pleural fluid was defined as exudates if it fulfilled at least one of the following criteria: pleural fluid/serum ratio of total protein greater than 0.5; pleural fluid /serum ratio of total lactate dehydrogenase greater than 0.6; or pleural fluid lactate dehydrogenase greater than two-thirds of upper limit of normal for serum lactate dehydrogenase (i.e.,>400 IU/L).

Pleural effusion was attributed to heart failure when the patient had symptoms and signs of the left ventricular failure, echocardiography study revealed systolic or diastolic dysfunction of the left ventricle, and the pleural effusion responded to heart failure and diüretic therapy Echocardiography was not applied all of the patients. Echocardiography was done almost every patients (not all of them) who had symptoms and signs of the left ventricular failure and bilateral pleural effusions.

Malignant pleural effusion was diagnosed if the pleural fluid cytology or pleural biopsy findings were malign or if the patient had a persistent pleural effusion and a known malignancy and alternative diagnoses were excluded. Parapneumonic pleural effusion was defined as the clinical and radiological

diagnosis of pneumonia or positive bacterial culture in pleural fluid. Pleural fluid was categorized as tuberculous if Mycobacterium tuberculosis were found in pleural fluid or granuloma in pleural biopsy or an exudative lymphocytic effusion with high adenosine deaminase levels (>40 U/L) cleared in response to antituberculous therapy. Other diagnoses were established based on clinical and laboratory data.

Exclusion criteria

The following were excluded in the analyses: effusions of undetermined origin, effusions with more than one possible cause, empyema, and hemothorax.

Statistical analysis

Values are reported as the median (25th and 75th percentiles) since they were found not to be normally distributed. Mann-Whitney U test or Fisher exact test were used to assess the difference between different groups. The Spearman coefficient of rank correlation was used to assess the relation of plasma and pleural fluid NT-proBNP. To determine the diagnostic accuracy of NT-proBNP for heart failure, receiver operating characteristic (ROC) curve was analyzed and the area under curve (AUC) was calculated. Cut-off levels for pleural fluid NT-proBNP were derived from the ROC curve. A p-value of 0.05 or less was regarded as significant.

RESULTS

One hundred tweenty six patients with pleural effusions who were scheduled for diagnostic thoracentesis were consecutively included in the study. The median age of the study group was 59 years (min 18 years max:80 years). The causes of pleural effusions were as follows: malignancy 41 patients (32,53%), heart failure 39 patients (30.9%), parapneumonic 24 patients (19.0%), tuberculosis 11 patients (8.7%), others 11 patients (renal disease, liver cirrhosis, romatizmal diseases, collagen tissue disases..). Most patients with malignancy-associated pleural fluid had either primary or metastatic lung cancer.

Serum and pleural fluid NT-proBNP levels are shown in Table 1, together with LDH and protein levels. Patients with pleural effusion due to heart failure had significantly higher pleural fluid NT-proBNP levels than others (p< 0 .001) (Fig. 1). Pleural and serum NT-proBNP measures were closely correlated (r: 0.91, P<0.001, Fig. 2).

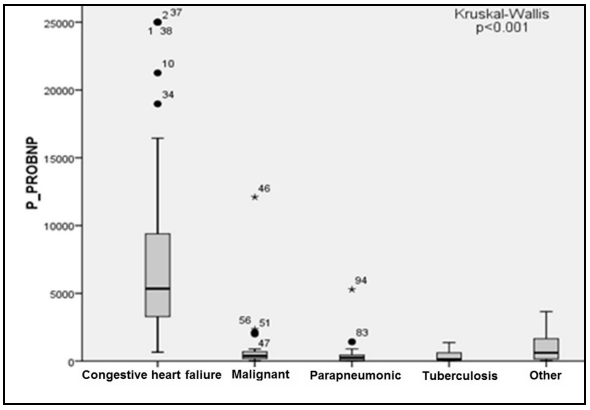

Figure 1. The median and quartiles of pleural NT-proBNP values according to etiology

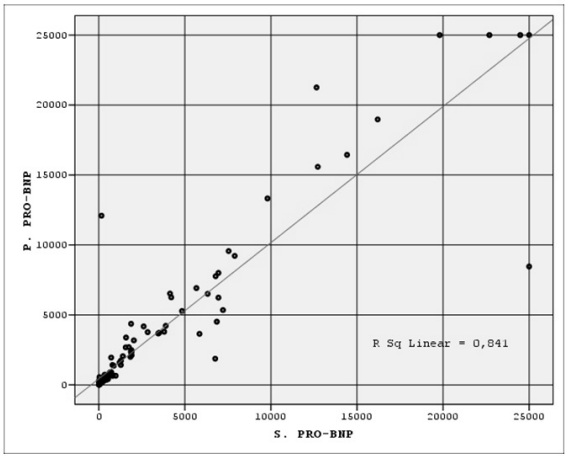

Figure 2. Correlation of serum and pleural effusion level of NT-proBNP

There were significant differences between blood and pleural fluid total protein levels, the

pleural fluid LDH levels, pleural fluid / blood LDH ratio, and serum- pleural fluid albumin difference among the groups. According to the criteria of Light et al (1), 88 of the pleural fluids were exudates. The distribution of causes of pleural fluid according to transudate or exudate is presented in Table 2. Using the above criteria, 1 effusion were incorrectly classified as exudates. This patient had pleural effusion due to heart failure. In this patient the heart failure was diagnosed by echocardiography and he had symptoms and signs of the left ventricular failure.

Receiver operating characteristic curve analysis (Fig. 3) demonstrated that an NT-proBNP cutoff value of 5133 pg/mL in pleural fluid had a sensitivity of 51.8%, a specificity of 98.9%, respectively (P=0.000, diagnostic accuracy 84.1%) for discriminating heart-failure-related transudates from non-heart-failure related pleural effusions.

Figure 3. Receive operating chacteristics curve of pleural fluid and serum NT-proBNP levels for differentiating true transudate from exudates. The area under the curve for pleural fluid NT-proBNP was 0,972 (95% CI 0,946 – 0,999) serum NT-proBNP was 0,973 (95% CI 0,949 – 0,997).

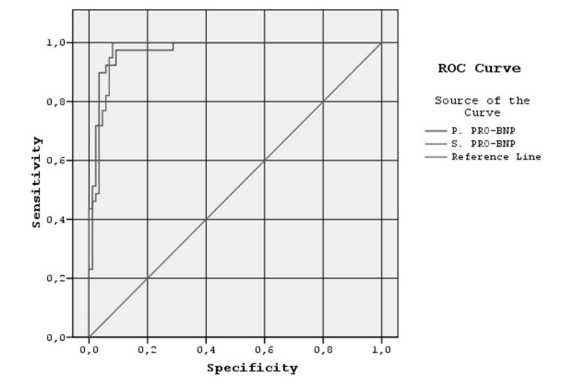

Table 1. Serum and pleural fluid characteristics of the subjets

	Heart failure	malignant	parapneumonic	tuberculasis	other	P
Serum						
NT-proBN P, median pq/ml	4210±2110	257,0 ± 198,1	168,2 ± 98,9	80,0 ± 28,9	503 ± 385,4	0,000
Protein, mean ± SD g/dl	6,4 ± 0,9	6,7 ± 0,9	7,0 ± 0,8	7,2 ± 0,7	7,2 ± 0,6	0,012
LDH	234,2 ± 83,9	345,3 ± 247,7	229,9 ± 109,8	223,1 ± 131,7	333,6 ± 235	0,013
Albumin	3,2 ± 0,5	3,3 ± 06	3,5 ± 0,6	3,5 ±,04	3,5 ±0,4	0,216
Pleural Fluid						
NT-proBN P	53462,3	380	248	129	612	0,000
Protein	2,3 ± 0,9	4,4 ±0,9	4,6 ± 0,7	5,2 ± 0,6	4,4 ± 1,2	0,000
LDH	108,4 ± 45,6	673,1 ± 629	396,9 ± 248	527,3 ± 477,7	499 ± 660	0,000
Albumin	1,3 ± 0,5	2,4 ± 0,5	2,60 ± 0,5	2,8 ± 0,4	2,7 ± 0,6	0,000
Pleural fluid/serum						
Protein ratio	0,3 ± 0,1	0,6 ± 01	0,6 ± 0,009	0,7 ± 0,005	0,6 ± 0,10	0,000
LDH ratio	0,5 ± 0,2	2,48 ± 2,7	1,9 ± 1,2	2,7 ± 2,1	2,0 ± 2,8	0,000
Abumine difference	19 ± 0,5	0,9 ± 0,3	09 ± 0,3	0,7 ± 0,1	1,1 ± 0,4	0,000

Table 2. Etiologies of pleural effusions, according to transudate or exudate, defined by the criteria of Light et al.

	Transudate		Exudate	
	n	(%)	11	(%)
Congestive heart failure	35	(92)	4	(4,5)
malignant	0		41	(46.6)
Parapneumonic	1	(2,6)	23	(26,1)
Tuberculosis	0		11	(12.5)
Others	2	(5=3)	9	(10,2)

DISCUSSION

Our study showed that both plasma and pleural fluid NT-proBNP levels were significantly higher in patients with heart-failure-associated pleural effusion, compared to others. Our results were in accordance with the recent studies that explored the diagnostic value of BNP and NT-proBNP in the etiology of pleural effusions (2-10). Porcel et al retrospectively examined 117 patients with pleural effusion and found that the pleural fluid levels of NTproBNP were significantly higher in patients with cardiac transudates than in patients with effusion of other causes (5). Tomcsa´nyi et al measured NT-proBNP levels in the pleural effusion of 14 patients with heart failure and 14 patients with different pleural pathology and found that heart-failure patients had significantly higher levels of NT-proBNP (4). In our study, patients with pleural effusion due to heart failure had significantly higher pleural fluid NT-proBNP levels than others and pleural and serum NT-proBNP measures were closely correlated. Median (25th to 75th percentiles) NT-proBNP levels of serum and pleural fluid

due to heart failure have been reported to be between 3227-10791 pg/ml (267-20.263) and 6295-10.427 pg/mL (3342-21.844), while median NT-proBNP levels of serum and pleural fluid related with non-cardiac reasons have been shown to be between 236-989 (296-1691) pg/mL and 277-947 pg/mL (372-1937) respectively (4,6-8)). Our results of NT-proBNP levels for pleural fluid and serum were also found in this range.

The pleural fluid NTproBNP or BNP cut-off values for discriminating pleural effusion with heart failure are variable from 1,176 pg/mL to 4,000 pg/mL (4,6-8). We found the pleural fluid NT-proBNP concentration of 5133 pg/mL to have a good accuracy for detecting pleural effusion with heart failure. Altuğ et al found that an NT-proBNP cutoff value of > 2,300 pg/mL in pleural fluid had a sensitivity of 70.8%, a specificity of 97.6%, and positive and negative predictive values of 94.4% and 85.4%, respectively, for discriminating transudates caused by heart failure from exudates in their study (10) .Tomcsa´nyi et al showed that the criteria of Light et al had a sensitivity of 93% and specificity of 43% for transudates (4). However, the pleural fluid NT-proBNP accurately differentiated between the 2 groups. Han et al (2) reported that 28 patients with pleural effusion due to heart failure were misclassified as exudates by the criteria of Light et al, (1) and suggested that pleural fluid NT-proBNP levels identified 26 of them correctly. In our study one patient was misdiagnosed as exudates according to the criteria of Light et al.(1) Pleural fluid NT proBNP level of one patient was significantly higher than those of true exudates.

Diuretic treatment is a possible explanation for biochemical exudates for heart failure. Diuretics may change a transudate into an exudate by shifting fluid from pleural space,

there by elevating the pleural levels of protein and lactate dehydrogenase (10). Pleural fluid NT-proBNP is suggested to be useful in the diagnosis of pleural effusion resulting from heart failure, especially in patients with exudates who are treated with diuretics. Han et al (2) reported that 26 of the 28 misclassified heart-failure patients received diuretics before thoracentesis and had pleural fluid NT-proBNP levels of higher than 1,714 pg/mL .

Our study has several limitations. First we excluded patients with effusions due to multiple etiologies. Our study sample was limited in size and we could not adjust NT-proBNP concentrations, which were shown to be influenced by several factors, including age, sex, renal function, anemia, and obesity. In patients with reduced renal function, BNP and NTproBNP values are increased with a negative correlation to creatinine clearance (11).

In our study, serum and pleural fluid NT-proBNP concentrations were found to be significantly correlated. Kolditz and colleagues have pointed out that plasma and pleural fluid NT-proBNP levels had similar diagnostic accuracy, which confirmed another study that had demonstrated a high correlation also (6). Therefore, in case of risk diagnostic thoracenthesis, plasma NTproBNP measurements could be used as a predictor of cardiac originated pleural effusions. Another finding supporting this suggestion is the lower concentrations of NT-proBNP in non-cardiac originated pleural transudates (7). We found serum and pleural fluid NTproBNP levels to be higher in transudates and this reached statistically significance for pleural fluid.

High level of pleural fluid NT-proBNP in heart failure may be important in terms of clinical use. But the cost in terms of effectiveness use of the pleural fluid NT-proBNP, instead of each patient, It would be better to use the NT-proBNP in patients who had the symptoms of heart failure, exudative pleural fluid and use of diüretics. Many studies are needed about the cost effectiveness of pleural fluid.

Our results suggest that the inclusion of pleural fluid NTproBNP measurement in thoracentesis would enhance discrimination among the different causes of pleural effusion especially for congestive heart failure cases. The test may be especially useful in heart failure patients with exudates pleural fluid.

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