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ORIGINAL ARTICLE

The Investigation of the Effect of Electrolyte Disorder on Sweat Test in Newborns with Positive Cystic Fibrosis Screening

Kistik Fibrozis Taraması Pozitif Yenidoğanlarda Elektrolit Bozukluğunun Ter Testine Etkisinin Araştırılması

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ABSTRACT

Background and objectives: The aim of this study is to investigate the effect of the electrolyte and acid-base status present at the time of admission to the hospital on the sweat test (ST) of the patients who were found to have a positive newborn screening test (NST) for Cystic Fibrosis (CF).
Methods: The patients who referred to pediatric pulmonology clinic for ST with positive NST for CF and diagnosed as CF were analyzed retrospectively. From the medical records, acid-base status measured simultaneously with the ST and with serum sodium, potassium, and chloride levels were included in the study.
Results: The study was completed with 37 patients who met the inclusion criteria. At the time of ST, the mean sodium, potassium and chlorine values were 134.83±4.25 (122.0-141.0), 4.94±0.95 (2.9-7.6) and 97.72±12.40 (64.0-116.0) mEq/L, respectively. Patients whose electrolytes were measured at the time of diagnosis, 27.0% (n=10) had hyponatremia, 8.1% (n=3) had hypokalemia, and 4.8% (n=1) had hypochloremia. There was a significant difference between serum chloride and bicarbonate levels according to the negative, borderline and positive ST groups (p=0,036). In addition, no significance was detected between the sweat test values of patients with and without Pseudo-Bartter Syndrome (PBS) (38.7%).
Conclusion: This study shows that the electrolyte disorders, low Na, Cl values and higher pH and HCO3' values than normal at the time of ST affects the ST results. So, it is important to check the serum electrolyte levels before ST of the NST positive newborn.

Keywords: Cystic fibrosis, Sweat test, Newborn screening, Serum electrolytes, Pseudo-Bartter syndrome.

ÖZ

Giriş ve Amaç: Kistik Fibrozis (KF) yenidoğan tarama testi pozitif olup ter testi yapılması için yönlendirilen hastaların başvuru anındaki elektrolit ve kan gazı değerlerinin ter testi üzerindeki etkisini araştırmak.
Yöntemler: Çocuk göğüs hastalıkları polikliniğine kistik fibrozis için yenidoğan tarama testi pozitif olan ter testi nedeniyle başvuran ve kistik fibrozis tanısı almış olan hastalar retrospektif olarak incelendi. Tıbbi kayıtlarda ter testi ile eş zamanlı ölçülen asit-baz değerleri, serum sodyum, potasyum ve klorür düzeyleri olan hastalar çalışmaya dahil edildi.
Bulgular: Çalışma, dahil edilme kriterlerini karşılayan 37 hasta ile tamamlandı. Ter testi sırasında ortalama sodyum, potasyum ve klor değerleri sırasıyla 134,83±4,25 (122,0-141,0), 4,94±0,95 (2,9-7,6) ve 97,72±12,40 (64,0-116,0) mEq/L idi. Tanı anında elektrolitleri ölçülen hastaların %27,0'ında (n=10) hiponatremi, %8,1'inde (n=3) hipokalemi, %4,8'inde (n=1) hipokloremi vardı. Negatif, borderline ve pozitif ter testi gruplarına göre serum klorür ve bikarbonat düzeyleri arasında anlamlı fark vardı (p=0,036). Ayrıca Psödo-Bartter Sendromu (PBS) (%38,7) olan ve olmayan hastaların ter testi değerleri arasında anlamlılık saptanmadı.
Sonuç: Bu çalışma, ST anında elektrolit bozukluklarının, düşük Na, Cl değerlerinin, pH ve HCO3' değerlerinin normalden yüksek olmasının ST sonuçlarını etkilediğini göstermektedir. Bu nedenle NST pozitif yeni doğanın ST öncesi serum elektrolit düzeylerinin kontrol edilmesi önemlidir.

Anahtar Kelimeler: Kistik fibroz, ter testi, yenidoğan taraması, serum elektrolitleri, psödo-Bartter Sendromu.

Introduction

Cystic Fibrosis (CF, OMIM#219700) is caused by a defect in the chloride channel called the CF transmembrane conductance regulator (CFTR) which is essential for the normal function of the epithelium in the airways, intestinal lumen, pancreas, testicles and sweat glands (1). The CF patients had the clinic of metabolic alkalosis defined by the increase of both plasma HCO3 level (>26 mmol/L) and blood arterial pH (>7.43) which is quite frequent and usually accompanied by hypokalemia. Its pathogenesis requires both the generation of alkalosis and its maintenance (2).

The presentation of CF is often due to chronic respiratory and gastrointestinal symptoms. However, in infants Pseudo Bartter syndrome (PBS), which is a symptom of dehydration accompanied by severe electrolyte and acid-base disturbances, may be the primary presentation especially in regions with hot climates (3-6).

PBS is known as complication of CF which is consisted of hyponatremic, hypochloremic dehydration with metabolic alkalosis without renal pathology. On the other side, Bartter Syndrome (BS) is a rare autosomal recessive disease accompanied by salt absorption disorder in the thick ascending limb of loop of Henle.

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It is generally characterized by normal blood pressure despite metabolic alkalosis, hypokalemia, hypercalciuria, and increased renin-aldosterone ratio (7).

CF was included in the newborn screening program by the Ministry of Health in 2015 in Turkey (7,8). Taking into account PBS accompanying CF in the literature especially in countries with a Mediterranean climate like Turkiye, it may be necessary to check electrolyte along with sweat test at the first diagnosis (6). Although it is not in the routine algorithm, serum sodium, potassium, chloride and acid-base status should be checked simultaneously. Because the low level in these electrolytes, especially in chloride, directly affects ST; and other low electrolyte levels affect the ST when sweat conductivity test is performed and this situation may cause the results to be normal (false negative) or in intermediate value. Although there are publications drawing attention to this issue, there are no studies that can constitute a basis for the need to examine sodium, potassium, and chloride and acid-base status simultaneously. The aim of this study is to investigate the effect of electrolyte and acid-base status on the ST of patients with positive NST and referred for ST.

Material and Methods

In this retrospective study, the files of the patients, who were referred to Necmettin Erbakan University Medical Faculty (NEUMF), Pediatric Pulmonology and whose sweat tests were performed after a high Immunoreactive Trypsinogen (IRT) value was detected in the NST and diagnosed as CF, were reviewed between January 2015 and December 2017. Children whose first blood IRT value was higher than 90 and the second IRT was higher than 70 were evaluated for CF and ST (8,9). The study was approved by the Ethics Committee of NEUMMF (Number: 2019/1826 Date: 10.05.2019).

Demographic data (age, gender), weight at diagnosis, month of admission to the polyclinic, family history (kinship between parents, siblings with CF), the IRT value evaluated in the heel prick screening test, the history of meconium ileus and jaundice, electrolyte levels (Na, K, Cl) measured simultaneously with the ST, arterial acid-base status (pH, HCO3) and the results of the ST was collected and evaluated.

Conductivity measurement was used in the ST with the method available in the hospital. In the evaluation, less than 50 mmol/L was considered negative, 50-90 mmol/L was borderline and above 90 mmol/L was positive (8). In heel prick screening test results of newborns, IRT-1 ≥90 ng/ml and IRT-2 ≥70 ng/ml were considered as positive (8,9). Normal ranges of serum values were accepted as 135-145 mEq/L for sodium, 98-107 mEq/L for chloride, 3.5-5.1 mEq/L for potassium. The normal pH values measured in acid-base status was 7.35-7.45 and the bicarbonate value between 21-27 mEq/L was accepted as normal (10,11).

Inclusion Criteria: Patients diagnosed with CF (patients with one or more clinical features of CF and with ST ≥90 mEq/l and patients diagnosed by showing two mutations for patients with normal or borderline ST with at least one clinical feature of CF, patients detected as positive in newborn screening, patients who underwent ST (ST is performed by Macroduct method) were included in the study.

1- Patients diagnosed with CF (Patients diagnosed by showing two mutations for patients with one or more Cystic Fibrosis clinical features and sweat test >90 mEq/l and for patients with at least one Cystic Fibrosis clinical feature with normal or borderline sweat test) were included in the study. (Sweat test is done by Macroduct method).)

2- Patients with positivity in newborn screening

3- Patients who underwent sweat test

4- Patients who come to the controls regularly. Cut off levels were defined according to the study of Sismanlar et.al. (6). They reported that according to the receiver operating characteristic (ROC) curve graph, the best conductivity cut-off value to make the CF diagnosis was 90 mmol/L and to exclude the CF diagnosis was 70 mmol/L. They suggested the conductivity measurement as a reliable and quantitative sweat chloride analysis to diagnose or exclude CF which can be used as a diagnostic test in addition to screening (6).

Exclusion Criteria: The patients whose heel prick screening test results could not be obtained or were not performed, the patients whose ST were postponed due to severe electrolyte disorder (especially hyponatremia) at the time of admission were excluded.

Data entry, statistical analysis and report writing processes were done in computer environment. SPSS for Windows version 15.0 (SPSS Inc., Chicago, IL, USA) package program was used in the analysis. In summarizing numerical data; arithmetic mean, standard deviation, median, minimum and maximum values, frequency distributions and percentages were used to summarize categorical data. Relationships between data; Chi-square test, Mann-Whitney U test, Kruskal Wallis analysis of variance and Spearman correlation coefficient were used. Statistical significance was accepted as $p < 0.05$.

Results

There were 52 children diagnosed with CF but after the exclusion, the study continued with 37 patients. The 48.6% were girls (n=18) and there was a consanguinity between the parents of 29.7% (n=11). History of CF in siblings was 18.9% (n=7). The median age of diagnosis was 43 (11-366) days. The mean body weight at the time of diagnosis was 4345 ± 1480 (2030-10600) grams, and 72.3% (n=27) of them had weight-for-age below the 50% percentile.

CF NST of all patients included in the study was positive. At the time of admission to the hospital, 14 (43.75%) of the screened patients had a positive ST. The ST results of 14 (43.75%) patients were at borderline. There were five patients who did not sweat. The second ST

of 36.4% (n=4) of 14 patients with borderline ST was positive, and second ST of 36.4% (n=4) of the patients was at borderline. There were three patients who did not sweat.

When the ST and electrolyte levels were compared according to the seasons they were diagnosed, no significant difference was found between them (p>0.05). Patients whose electrolytes were measured at the time of diagnosis, 27.0% (n=10) had hyponatremia, 8.1% (n=3) had hypokalemia, and 4.8% (n=1) had hypochloremia. It was determined that 10.0% (n=3) of the patients had low pH and 36.7% (n=11) of the patients had high pH, that is, alkalosis. The bicarbonate level was found low in 13.3% (n=4) patients and high in 40.0% (n=12) patients. The mean of IRT, ST, and the electrolyte and acid-base status performed in the newborn screening is given in Table I, Table II shows the levels of ST, IRT and electrolytes of the study group.

IRT-1, IRT-2 values and chloride and bicarbonate levels according to patients' ST groups (negative, borderline, positive) were significantly different (p=0.010, p=0.001, p=0.036, p=0.048 respectively). Patients with positive ST had significantly higher IRT-1 and IRT-2 values. Chloride values were lower in the group with negative ST. In the first ST, one of the six patients with low chlorine value had a negative ST while four had intermediate and one had normal (Table-III).

At the time of admission, 38.7% (n=14) of the patients were in the PBS picture and 50% (n=7) of them were female. There was no significant difference between genders (p>0.05). Age-weight percentiles of 64.2% (n=9) of the patients were below 50% percentile. While 35.7% (n=5) had a sibling history with CF, consanguinity between the parents was 14.2% (n=2).

According to newborn heel prick screening test and ST there were no significant difference between the patients with and without PBS (p>0.05). Potassium and chloride values were significantly different (p=0.002, p=0.022) and potassium and chloride values were lower in the group with PBS. Bicarbonate level was significantly higher in the group with PBS (p=0,028). Some comparisons between the two groups are given in Table IV.

Table I. The median of IRT, ST and electrolyte values

	Avg±SD**	Median (Min-Max)
IRT-1* value	197.0±111.33	172.0 (69.0-565.80)
IRT-2* value	156.44±86.35	130.0 (39.0-368.0)
First sweat test result	77.73 ±24.14	87.30 (9.30-111.0)
Second sweat test result	70.30±30.85	82.50 (12.50-108.94)
Sodium (mEq/L)	134.83±4.25	136.0 (122.0-141.0)
Potassium(mEq/L)	4.94±0.95	5.0 (2.90-7.60)
Chloride(mEq/L)	97.72±12.40	102.0 (64.0-116.0)
Magnesium(mEq/L)	2.16±0.30	2.09 (1.56-2.77)
pH	7.44±0.08	7.44 (7.27-7.65)
HCO3	27.94±8.61	25.90 (14.80-52.60)

* IRT: (Immunoreactive Trypsinogen) Value in newborn heel prick screening

**SD: Standard deviation

Table II: Comparison of IRT electrolyte and acid- base status according to the results of the first sweat test

Parameters		1.Sweat Test 0-50: Negative n(%)	50-90: Borderline n(%)	90 and above: Positive n(%)	Total n(%)
1.IRT* value	Negative	0 (0.0)	1(100)	0 (0.0)	1(100)
	Positive	4(12.9)	13(41.9)	14(45.2)	31(100)
2.IRT* value	Negative	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Positive	4(12.9)	13(41.9)	14(45.2)	31(100)
Sodium	Low	1(11.1)	7(77.8)	1 (11.1)	9(100)
	Normal	3(13.0)	7 (30.4)	13(56.5)	23(100)
	High	0 (0.0)	0 (0.0)	0 (0.0)	0(0.0)
Potassium	Low	1(50.0)	0(0.0)	1(50.0)	2(100.0)
	Normal	1 (6.2)	10(62.5)	5(31.2)	16(100.0)
	High	2(14.3)	4(28.6)	8(57.1)	14(100.0)
Chloride	Low	1(16.7)	4(66.7)	1(16.7)	6(100.0)
	Normal	3(12.0)	10(40.0)	12(48.0)	25(100.0)
	High	0(0.0)	0(0.0)	1(100.0)	1(100.0)
Magnesium	Low	0(0.0)	0(0.0)	0(0.0)	0(0.0)
	Normal	3(18.8)	5(31.2)	8(50.0)	16(100.0)
	High	0(0.0)	0(0.0)	1(100)	1(100)
pH	Low	1(50.0)	0(0.0)	1(50.0)	2(100.0)
	Normal	1(7.1)	5(35.7)	8(57.1)	14(100.0)
	High	1(11.1)	5(55.6)	3(33.3)	9(100.0)
HCO3	Low	0(0.0)	0(0.0)	4(100.0)	4(100.0)
	Normal	1(9.1)	5(45.5)	5(45.5)	11(100.0)
	High	2(20.0)	5(50.0)	3(30.0)	10(100.0)

Table III. Averages and comparisons of the first sweat test result with the condition of the IRT, electrolyte levels and acid-base status.

	First Sweat Test Average±SD* 0-50 (negative)[a]	50-90 (borderline)[b]	90 and more (positive)[c]	p
IRT-1** value	124.83±28.01	161.99±86.68	254.05±123.32	0.046[ac] 0.034[bc] (0.010)
IRT-2** value	85.01±16.75	118.59±38.79	221.12±87.52	0.003[ac] 0.017[bc] (0.001)
Sodium (mEq/L)	135.75±1.89	133.71±5.33	135.79±3.33	0.541
Potassium (mEq/L)	4.79±1.04	4.76±0.62	5.34±1.12	0.238
Chloride (mEq/L)	94.50±9.85	95.07±12.25	101.07±10.99	0.036
pH	7.45±0.15	7.45±0.6	7.42±0.08	0.626
HCO3	28.63±6.07	31.60±9.7	23.88±6.59	0.050[bc] (0.048)

*SD: Standard deviation

** IRT: Value (Immunoreactive Trypsinogen) in newborn heel prick screening

Table IV: Numbers and percentages of newborn sweat test screening results of the groups with and without PBS

PBS presence	Negative	Positive	P
	Average±SD**	Average±SD**	
Age at diagnosis	69±74	53±44	0.301
Diagnostic weight	4220±1778	4221±829	0.616
Week of birth	37±3	39±1	0.330
Birth weight	3059±539	3243±339	0.296
IRT-1 * value	185±87.08	215.39±144.60	0.719
IRT-2* value	155.99±90.79	157.15±82.23	0.615
First sweat test	77.54±26.76	78.03±20.11	0.741
Second sweat test	71.34±32.05	68.22±30.3	0.554
Sodium(mEq/L)	136.35±1.30	132.36±6.06	0.114
Potassi-um(mEq/L)	5.29±0.68	4.38±1.07	0.002*
Chloride(mEq/L)	103.13±4.27	88.86±14.08	0.022*
pH	7.42±0.06	7.47±0.11	0.078
HCO3	24.86±3.59	31.97±11.45	0.028*

*IRT: Value (Immunoreactive Tripsinojen) in newborn heel prick screening

**SD: Standard deviation

Discussion

CF is a metabolic disease with high mortality and morbidity. With early diagnosis, regular follow-up and compliance with treatment, the quality of life and lifespan of the cases increase. This study was conducted on electrolyte disorder which is one of the conditions that can affect the result of the ST, which is a very important test in diagnosis. It is also the first study because it does not investigate the effect of electrolytes on the ST by examining the serum electrolytes of the child before performing the ST after screening, and it tries to explain this effect. The results of the study will contribute significantly to further studies to be carried out on this subject, since there are limited studies on the search for the reasons that may affect the result of the ST.

The median age at diagnosis was 43 days, and all cases were diagnosed before the age of one year. European Cystic Fibrosis Society 2008-2009 data reported that 60% of the cases were diagnosed in the first year (13). A study in Iran in 2010, reported the median age at diagnosis as 5 months (14). The reason for the high rate of diagnosis under the of age one year in this study was considered as the inclusion of patients with positive CF screening.

ST and electrolyte levels were not different according to the seasons. It should be kept in mind that ST results may be false negative, especially in hot climates and in winter dressing warmly when room temperature is extremely high.

Chloride measurement in sweat is the gold standard for diagnosis. In a study conducted on ST results, 12% false negative and 15% false positive results were found (15) Hypochloremia was detected in 27.0% (10 patients) of 37 patients who came for screening without any complaints, and chlorine values were determined as 97.72±12.40 (64.0-116.0) mEq/L. Likewise, the results of the first ST were negative in one of the 6 patients with a low chlorine value, and an intermediate value was detected in 4 of them although these children were diagnosed with definite CF in the follow-up. This suggests that regardless of the method of the ST, the electrolyte levels of the children with positive CF screening test should at least be evaluated even if blood gas cannot be measured at first visit. Other researchers state that low blood chlorine levels also cause low sweat levels (6). Accordingly, it was determined that blood electrolytes were also low in pseudo-Bartter syndrome in children with CF, in which there is excessive salt loss from the skin. In the ST measurements made at this time, the chlorine level in the sweat may be lower at the limit. In these patients, they recommended that blood chlorine measurement should be performed after blood electrolyte levels returned to normal (5,16). Similarly, at the time of admission 27.0% had hyponatremia, 8.1% had hypokalemia, 36.7% alkalosis and 40.0% had high HCO3 levels and these results shows definite CF although these children do not have obvious findings. It indicates that these changes in electrolyte values may affect the ST. Since this situation will delay the diagnosis of patients with a negative ST, it will not be possible for children to receive early treatment. This situation will also lead to a newborn with a high IRT being referred to a screening program and being misdiagnosed as not having CF. Detecting low chloride level with a negative result in sweat cannot exclude the diagnosis of CF (14). In this study, the ST of 43.8% of the cases was in the range of 50-90 mmol/L. Edmondson et al. (17) reported that 17% of the patients with negative ST results and positive newborn screening test were diagnosed with CF during the follow-up period. Because the clinical spectrum of CF is highly variable, the follow-up of the patients with positive screening tests, leading to negative and intermediate values on clinical suspicion, should continue. Intermittent sweat testing can help diagnose these patients. Although there were patients with CF in this study, not all ST results were positive. It should be kept in mind that PBS, which is a common complication in CF patients, or other electrolyte disturbances or other pathologies may be the reason that causes false negative. If the patients with positive heel prick screening test and negative ST need to be followed up for CF for a while, the diagnosis should be confirmed with further examinations. In the study, the difference between the ST, low serum chloride and the bicarbonate value at the time of admission was associated with the fact that these patients were in PBS picture at the time of admission or their low ST result due to electrolyte disorder. So, it is important to check the electrolyte levels while ST was being performed.

Chloride and bicarbonate levels according to their ST groups (negative, borderline, positive) were significantly different. Bicarbonate value was higher in the group with negative ST and in the borderline group compared to the group with positive ST while chloride levels were lower in the group with borderline and negative STs. It was thought that if patients

had hypochloremic metabolic alkalosis, this would cause the ST results to be false negative, and this is an important result. In the literature, there is no study comparing electrolytes and ST results. Knowing that normal serum electrolytes performed in the laboratory and clinic when these patients came for ST had an effect on ST, and ST is not considered only as a test suggests that the patient should be evaluated by the doctor first and the ST should be performed after the serum, chloride control, if possible. Otherwise, normal ST results of the patients in warmer countries like Turkiye than in northern European countries with high IRT values as a result of scanning may lead to delayed or misdiagnosis.

Some researchers did not find significant difference in ST of patients with and without PBS although the ST results of patients with PBS were higher (15,18). Similarly, Tutar et al. (19) did not find significant difference in ST in sweat chloride test values. However, in this study, the ST was not performed in children when they had PBS. Sismanlar et al. (6) reported that the first sweat chloride test value was not significantly lower in PBS patients, but the second sweat chloride test value was significantly lower in PBS patients. Similarly, although the mean of the second ST was lower in the group with PBS, the first and the second ST result of patients with PBS and without PBS were not different significantly.

PBS, a disease with hyponatremia, hypochloremia and metabolic acidosis, is a common complication in CF and often missed as simple dehydration or BS (20,21). The mean potassium and chloride values were significantly lower, the mean bicarbonate value was significantly higher in the patients with PBS. In favor of our findings a study with 2,664 patients, 16 children had sweat conductivity values higher than 80. Age, pH, HCO3, Na, Cl, K and the sweat conductivity test were found statistically related (22). The difference of our report is that ST was applied to the children who just came for CF screening test positivity. It is important in these children that the blood electrolyte values are in the normal range because the low level of electrolytes especially Na, K, Cl, is assumed to affect the ST. So, we think that before ST controlling serum electrolytes levels are important. Another important issue in this study is that the patients had a PBS picture when they applied for a ST after they had a positive screening test result even though there was no clinical symptom. This situation can be thought to cause the ST results to be normal or at borderline.

Since sweat testing is of great importance in the diagnosis of CF, blood electrolyte levels and acid-base status should be checked in patients before performing a ST and if an electrolyte disorder is detected, ST should be performed after correcting electrolytes. A study claims that the management of PBS is focused on rehydration and correction of electrolyte abnormalities in children with CF (4). However, when ST is performed regardless of electrolytes in hot countries like Turkiye, in an undetected electrolyte disorder, the ST may turn out to be false negative. In this case, the success of the newborn CF screening program will be affected and the patient's diagnosis will be delayed. False negativity causes a delay in diagnosis and affects the prognosis of patients by delaying treatment, which affects not only the patients and their families but the whole society. It causes deviations in the targeted results of the CF screening program in health services. In addition to adverse social and psychological impacts, increased health costs and improper use of the health workforce have both national and international impacts.

In very hot weather, PPH and electrolyte abnormalities may be seen even in elderly cystic fibrosis patients (23). Main limitation of the study may be seen as making the diagnose via conductivity ST for sweat chloride test, but Mattar et al. (22) says that this way of testing is as accurate as sweat chloride test for the diagnose of CF. Similarly, in another study in Turkiye with a high number of participation, authors used this way of testing (24). The second limitation is the number the patients with full records showing the importance of patient follow up and recording.

Conclusion

In conclusion, infants with positive CF screening test and no symptoms referred for ST may have low Na, Cl values, and higher pH and HCO3' values than normal at the time of ST. This study shows that the electrolyte disorder which is present during the ST affects the ST result. It is important to see that the electrolyte and blood gas values are normal before the ST is performed after CF scanning, and to perform a ST after that, regardless of the method. Thus, after the CF screening test, false normal ST results and negative CF diagnosis will be avoided. As we suggested here, all can be prevented via simple, cost-free attention.

Ethics statement: The study was approved by the Ethics Committee of Necmettin Erbakan University Meram Medical Faculty (Number: 2019/1826 Date: 10.05.2019).

Conflict of interest: There are no competing interests.

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