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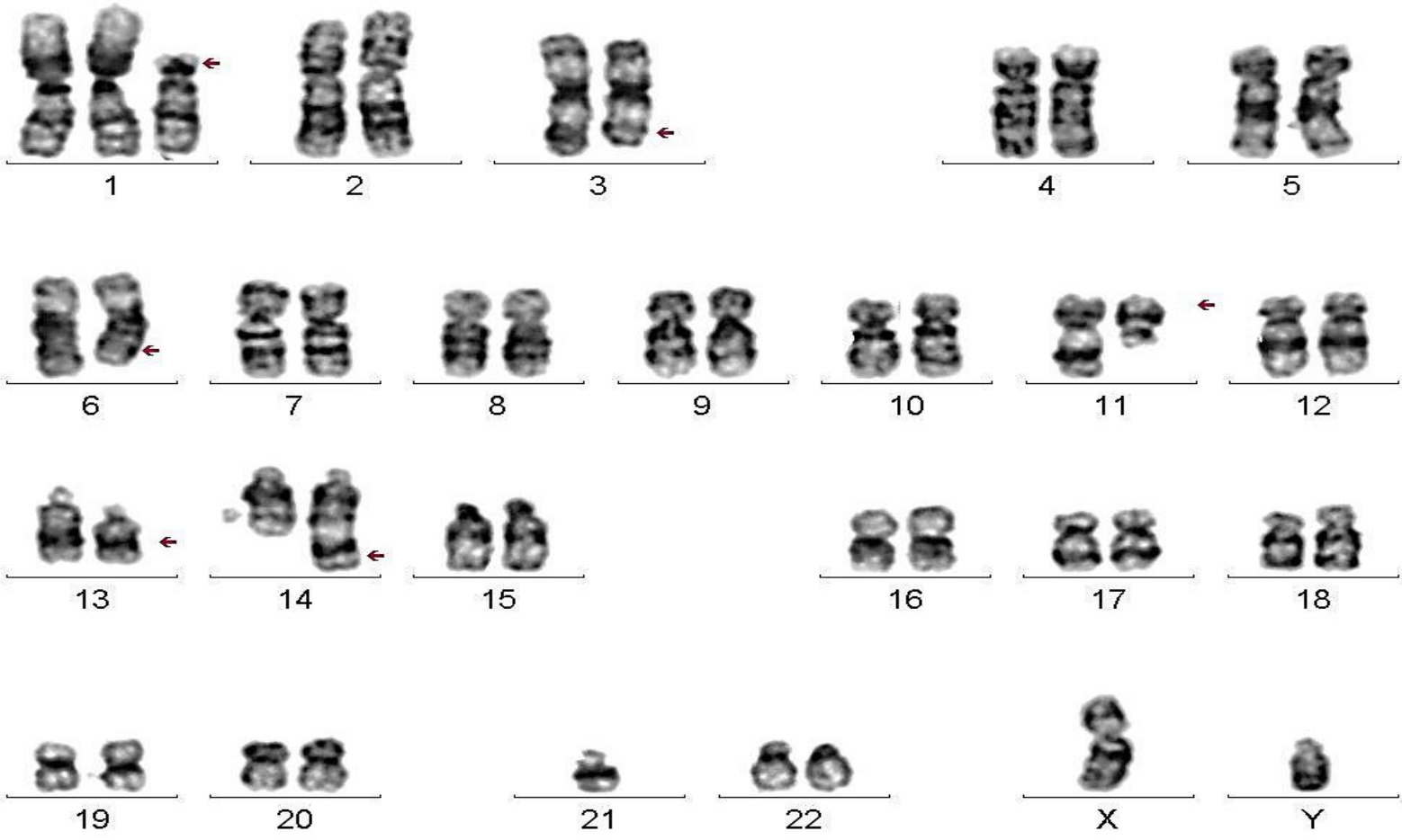

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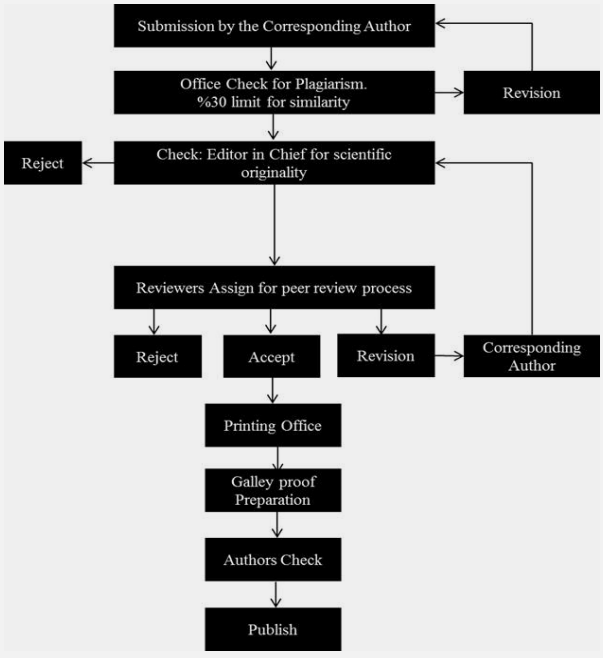

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Do antiepileptic drugs have any effect on Neutrophil / Lymphocyte and Platelet / Lymphocyte Ratio?

İlhan Çağ[1], Yaşar Altun[1]*, Erman Altunışık[1]

Abstract

Objective: The aim of this study was to compare the complete blood count values of 40 healthy individuals and 60 patients who are using antiepileptic drugs (AEDs), specifically to evaluate neutrophil-lymphocyte ratio (NLR), monocyte-lymphocyte ratio (MLR), platelet-lymphocyte ratio (PLR), and basophil-lymphocyte ratio (BLR). This study is important because it is the first study on hematological parameters such as NLR, MLO, PLO and BLO.

Material and Methods: In this study, hemogram and biochemical data of 17 patients who received carbamazepine (CBZ), 21 patients with valproic acid (VPA), 22 patients with levetiracetam (LEV) along with 40 healthy controls were gathered and compared. The differences between the groups were evaluated statistically.

Results: No difference was present between the groups in terms of age or gender ($p > 0.05$). NLR was 2.19±1.42 for patients using CBZ, 1.64±1.34 for VPA users, 2.18±0.73 for LEV users and 2.04±0.85 for control group ($p > 0.05$). NLR, MLR, PLR and BLR were not significantly different from the control group.

Conclusion: To our knowledge, no study has targeted the haematological effects of antiepileptics on NLR, MLR, PLR and BLR. This study was important because it is the first study the effect of various antiepileptics on the hematological parameters such as NLR, MLR, PLR, and BLR. We believe that our study will articulate new studies.

Keywords: Antiepileptic drugs, NLR, PLR

Introduction

The thrombocytopenia effect of valproic acid (VPA) is a well-known and extensively investigated chemical, and it has been demonstrated to have negative effects on coagulation cascade, especially von Willebrand factor such as factor VIII and XIII, and platelet function resulting serious bleeding diathesis (1). Side effects of antiepileptic drugs (AEDs) such as VPA, levetiracetam (LEV), and carbamazepine (CBZ) on blood parameters have been demonstrated (2,3). Although the effects of these AEDs on blood values are well known, their effects on neutrophil-lymphocyte ratio (NLR), monocyte-lymphocyte ratio (MLR) and platelet-lymphocyte ratio (PLR) are unknown. Earlier studies have elaborated the role of epilepsy in hematopoiesis and its effects on individual blood cell biology and hemorheological characteristics (4-6). Information on the effect of AEDs used in epilepsy on red blood cells is inconsistent. Suwalsky et al. reported a decrease in the number of red blood cells (RBC) in anti-epileptic drug (AED) users compared to control subjects (7), but Beyazıt et al. (8) reported no difference.

Complete blood count (CBC) is simple but contains important follow-up parameters for many diseases (9). In addition, White blood cell (WBC) count and WBC subtypes are commonly used as inflammatory markers. Recently, however, the NLR has emerged as a new marker of systemic inflammation. The NLR is an easily available parameter with CBC and is relatively inexpensive (10). Among the parameters of the haemogram, the erythrocyte distribution width (RDW_CW) is a measure of the distribution of erythrocytes based on the diameter or volume. RDW is a coefficient of variation and is calculated by one standard deviation from the mean erythrocyte volume (MCV) X 100 formula. The association of RDW levels with inflammatory processes has been demonstrated in extensive cohort studies (11). NLR and PLR are cheap and easily computable indices that correlate with the prognosis of systemic inflammatory diseases (12). Platelets are cell fragments involved in the formation of blood clots, which are also related to inflammatory events.

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Mean platelet volume (MPV) and platelet distribution width (PDW) are commonly used to estimate the functional changes and activation of platelets. MPV may increase with acute myocardial infarction, renal artery stenosis, and preeclampsia. Changes in platelet function are expected in neurological disorders such as acute ischemic stroke and intracerebral hemorrhage (13-15). WBC produced in the bone marrow is the disease-fighting agents of the immune system. Neutrophils and lymphocytes are the most important components of the inflammatory response (16). Antiepileptic drug use may affect these immune cells both directly and indirectly and may regulate their function. Neutrophil-lymphocyte ratio and PLR are the parameters available for inflammation markers. The use of high NLR as a prognostic factor in cardiovascular diseases, cancers and autoimmune diseases is investigated (17). PLR was reported to be an independent predictor of overall survival (18).

Using hematological parameters is an easy and inexpensive method when obtaining accurate information from patients is not possible (19). NLR and PLR are the values obtained by the combined calculation of two of the CBC parameters and recently investigated on various other conditions. The ratios are important because they are derived from two different blood parameters (12). These are limited data on the haematological effects of antiepileptics related to NLR, PLR, neutrophil (NEU), lymphocyte (LYM), monocyte (MONO), basophil (BASO), and eosinophil (EOS) percentages. To our knowledge, the MLR and basophil-lymphocyte ratio (BLR) have not been investigated in depth. Studies involving the association of MLR with various cancers are present and were reported to be an independent prognostic factor (12,13,19). Although we are aware of the association of MLR with various diseases, we did not find any study in the literature reporting the role of MLR in AED users. In this study, we aimed to investigate the CBC values along with NEC, PLR, BLR, and MLR together with their diagnostic values.

Material and Methods

In this study, CBC, especially WBC, RBC, HGB, HTC, mean corpuscular volume (MCV), RDW_CW, platelet count (PLT), MPV, NEU, LYM, MONO, EOS and BASO values were evaluated. Seventeen individuals (7 females, 10 males, mean age: 32.24±11.38 years) receiving CBZ monotherapy, 21 individuals (5 females, 16 males, mean age: 31.19±11.73 years) with VPA monotherapy, and 22 individuals (14 females, 8 males, mean age: 32.46±18.61) with LEV monotherapy were selected as cases. All of the patients were admitted to and being followed-up at Adiyaman University Education and Research Hospital, Epilepsy Polyclinic.

A total of 40 healthy individuals (19 females, 21 males, mean age: 30.48±10.55) without any history of disease or drug use were included in the study as the control group. NLR, PLR, BLR and MLR ratios were compared between the patient groups and control group. The mean duration of drug use of CBZ, VPA, and LEV group was three months. Patients with CBZ, VPA and LEV and were included in the study did not received any other AEDs.

Inclusion criteria were as follows: (a) selected individuals were between 15-45 years old and were able to do daily activities. (b) They were on a normal diet. (c) They had been using CBZ, VPA or LEV for at least 6 months. (d) They did not use any other other medication that would affect neutrophils, lymphocytes, and platelet metabolism. (e) They did not have a thyroid dysfunction. (f) They did not have a liver or kidney disease. (g) They did not use multiple AEDs. (h) All the females were at the premenopausal period with the regular menstrual cycles and no history of oral contraceptive drug use.

Exclusion criteria of the study were presence of systemic inflammatory diseases, hematological diseases, cancer, severe liver, heart or kidney failure or a history of surgery/major trauma in the past one month, leukocytosis (WBC> 12000) with a fever of 37.5 or above, infection in the last two weeks, and use of antibiotics, antiaggregants, anticoagulants or immune suppressants.

The control group consisted of 40 volunteers with similar age and gender to the experimental group and visited to our outpatient clinic between January 2018 and December 2018 for reasons other than cerebrovascular disease and epilepsy and without any systemic disease. Ethics committee approval (2018/5-27) for the study was obtained from Adiyaman University Ethics Committee. In this study, the missing data about the patients were gathered by contacting the patients or their relatives from the telephone numbers registered in the system. Patients who could not be contacted for the missing data were excluded from the study.

Hematological analysis

Venous blood samples were obtained from the antecubital veins of both the patient and the control group between 08:00 and 10:00 after fasting for at least 8 hours. Samples were centrifuged in 30 minutes and on the same day centrifuged on the CELL-DYN 3700 SL analyzer (Abbott Diagnostics, Chicago, USA) in the biochemistry laboratory of Adiyaman University Education and Research Hospital. The reference intervals were determined as PLT: 142-424 (103/uL), MPV: 6.8-10.8 (fL), MCV: 80-97 (fL), RDW_CW: 11.6 -15.8 (%).

Statistical analyses

The data obtained from the study were uploaded to SPSS program (Ver: 22.0). Mean, standard deviation, median, lowest and highest frequency values and ratios were estimated as descriptive statistics of the data. The distribution of variables was measured by Kolmogorov Simirnov test. Mann-Whitney U test was used for the analysis of quantitative data. Chi-square test was used for the analysis of qualitative data and Fisher exact test was used when the chi-square test criteria was not met. The effect of NLR and PLR as a prognostic marker in epileptic patients was investigated by univariate and multivariate logistic regression analyzes. In addition, the rates associated with lymphocytes were compared between two groups. A value less than 0.05 was considered statistically significant.

Results

The daily drug dose was between 400-1200 mg/day in the CBZ group. The daily drug dose of patients using VLP ranged between 500-1500 mg/day. The daily dose of medication was between 500 and 1500 mg/day for the cases using LEV. Patients who received CBZ, VPA or LEV monotherapy were compared with the control group.

There was no statistically significant difference in age or gender between the patients and controls (p>0.05) (Table 1). The mean age was 32.24±11.38 in CBZ group, 32.16±11.73 in VPA group, 32.46±18.61 in the LEV group, and 30.48±10.55 in the control group (Table 2). No significant difference was found in age of CBZ and VPA patients in in comparison to the control group, but significant difference was found in patients with LEV (Table 2). The hematological parameters of the patient and control groups are demonstrated in Table 2.

The NLR values were 2.19±1.42 in the CBZ group, 1.64±1.34 in the VPA group, 2.18±0.73 in the LEV group and 2.04±0.85 in the control group. The MLR values were 0.24±0.10 in the CBZ group, 0.27±0.31 in the VPA group, 0.26±0.09 in the LEV group, and 0.24±0.16 in the control group. The BLR values were 0.03±0.01 in the group using CBZ, 0.03±0.02 in the VPA group, 0.04±0.04 in the LEV group, and 0.04±0.06 in the control group. There was no significant difference between the monotherapy drug users and control group for NLR, MLR and PLR (p>0.05).

PLR values were 100.03±40.85 in the CBZ group, 79.78±30.30 in the VPA group, 112.70±35.61 in the LEV group, and 97.86±29.70 in the control group. Although PLR values were higher in CBZ and LEV group compared to the control group, the difference was not statistically significant (p>0.05).

There was a statistically significant difference in PLT level between the experimental cases and control groups (p<0.05). Furthermore, RDW_CW values were significantly lower in cases with VPA and LEV (p<0.05), but was not same in patients using CBZ. There were no significant differences in Hgb, WBC, HTC, NLR, PLR, MLR and MPV values in patient and control groups (p>0.05) (Table 2). Neutrophil, lymphocyte and platelet levels were not significantly different in the patients who received medication compared to the control group and three-month post-medication (p>0.05). In patients using CBZ, HTC and MPV levels were found to be significantly higher after three-month treatment in comparison to those obtained from pretreatment (p<0.05). PLR values were significantly lower in patients with three-month VPA treatment compare to the pretreatment (p<0.05) (Table 3). In the group using VPA, the MPV and HTC levels were significantly lower in the three-month CBZ group than pretreatment (Table 3).

Table 1. Demographic characteristics of the patients (n: 100)

Parameter		Patients group (n: 60) (%)	Control group (n: 40) (%)	P value
Gender	Male	26 (43.3)	19 (47.5)	0.682
	Female	34 (56.6)	21 (52.5	
Age* (year)		31.95±14.33	30.48±1055	0.578

*Data presented as mean ± Standard deviation

Table 2. Comparison of socio-demographic variables and complete blood count values of antiepileptic drugs user and control groups. (*p < 0.05)

	CBZ	P value	VPA	P value	LEV	Control	P value
Age (years)	32.24±11.38	0.76	31.19±11.73	0.27	32.46±18.61	30.48±10.55	**0.03***
WBC (10^3/uL)	8.45±2.99	0.46	8.01±2.74	0.11	8.53±2.44	7.98±2.14	0.93
HGB (g/dL).	15.17±1.80	0.94	15.51±1.33	0.07	13.52±1.83	14.47±1.81	0.96
HTC (%)	44.40±4.56	0.52	45.81±3.30	0.05	42.27±5.33	43.54±4.61	0.33
NEU (10^6/uL)	5.00±2.23	0.66	4.17±1.91	0.24	5.18±1.92	4.76±1.83	0.40
LYM (10^3/uL)	2.58±1.19	0.61	2.94±1.14	**0.04***	2.47±0.68	2.46±0.67	**0.04***
PLT (10^3/uL)	227.22±60.48	**0.03***	213.77±63.61	**0.02***	260.87±51.59	223.91±37.23	**0.04***
MONO (10^3/uL)	0.56±0.16	0.49	0.65±0.38	0.11	0.62±0.14	0.53±0.18	**0.04***
EOS (10^3/uL)	0.21±0.17	0.13	0.17±0.03	0.47	0.15±0.09	0.15±0.09	0.84
BASO (10^3/uL)	0.09±0.05	0.73	0.09±0.04	0.84	0.09±0.07	0.08±0.06	0.56
NLR	2.19±1.42	0.52	1.64±1.34	0.97	2.18±0.73	2.04±0.85	0.28
PLR	100.03±40.85	0.30	79.78±30.30	0.65	112.70±35.61	97.86±29.70	0.28
MLR	0.24±0.10	0.98	0.27±0.31	0.28	0.26±0.09	0.24±0.16	0.56
BLR	0.03±0.01	0.70	0.03±0.02	0.52	0.04±0.04	0.04±0.06	0.93
MPV (fL)	7.31±1.14	0.06	7.94±1.60	0.25	7.22±1.37	8.90±2.11	0.08
RDW_CW (%)	11.84±0.86	0.06	11.81±0.84	**0.02***	12.02±0.10	12.46±1.48	**0.04***

Notes: CBZ: Carbamazepin; VPA: Valproate; LEV: Levetiracetam; WBC: White Blood Cell; HGB: Hemoglobin; HTC: Hematocrit; RDW_CW: Red Blood Cell Distribution Width Coefficent of Variation; PLT: Platelet; MPV: Mean Platelet Volume; NEU: Neutrophil; LYM: Lymphocyte; MONO: Monocyte; EOS: Eosinophil; BASO: Basophil; NLR: Neutrophil to Lymphocyte Ratio; PLR: Platelet to Lymphocyte Ratio; MLR: Monocyte to Lymphocyte Ratio; BLR: Basophil to Lymphocyte Ratio

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Table 3. Demographic data and hematological parameters of patients receiving monotherapy AED. In the group using VPA, the MPV and HTC levels were significantly lower in the three-month CBZ group (II) than pretreatment (I). (*p < 0.05)

	CBZ			VPA			LEV		
	I	II	P value	I	II	P value	I	II	P value
WBC (10^3/uL)	8.32±2.53	8.45±2.98	0.86	8.38±3.50	8.01±2.75	0.47	8.09±2.22	8.53±2.44	0.43
HGB (g/dL)	14.92±1.74	1.16±1.80	0.26	15.38±1.24	15.50±1.33	0.62	13.95±1.82	13.52±1.83	0.06
HTC (%)	44.40±4.56	45.90±5.29	**0.03***	45.81±3.30	46.99±4.41	0.15	42.27±5.33	41.21±5.27	0.17
NEU(10^6/uL)	4.76±1.62	5.00±2.22	0.70	5.25±3.63	4.17±1.91	0.11	4.78±2.10	5.18±1.92	0.47
LYM (10^3/uL)	2.57±1.20	2.58±1.19	0.96	2.38±0.71	2.94±1.14	0.07	2.50±0.78	2.47±0.68	0.81
PLT (10^3/uL)	233.77±53.61	227.22±60.48	0.26	229.42±73.07	213.77±63.61	0.11	271.25±67.91	260.87±51.59	0.26
MONO(10^3/uL)	0.66±0.28	0.56±0.16	0.23	0.52±0.16	0.65±0.37	0.16	0.57±0.15	0.62±0.14	0.19
EOS (10^3/uL)	0.21±0.19	0.20±0.16	0.82	0.16±0.12	0.17±0.13	0.56	0.17±0.12	0.15±0.09	0.13
BASO (10^3/uL)	0.11±0.08	0.08±0.04	0.09	0.07±0.03	0.08±0.04	0.11	0.07±0.02	0.09±0.06	0.19
NLR	2.13±0.98	2.19±1.42	0.89	2.58±3.01	1.63±1.34	0.21	2.07±1.07	2.17±0.73	0.67
PLR	102.17±34.15	100.03±40.84	0.85	104.84±44.08	79.78±30.30	**0.02***	112.46±25.44	112.70±35.61	0.97
MLR	0.27±0.08	0.24±0.09	0.30	0.22±0.06	0.27±0.31	0.46	0.25±0.13	0.25±0.09	0.88
BLR	0.40±0.15	0.35±0.11	0.22	0.28±0.11	0.31±0.18	0.68	0.29±0.11	0.39±0.38	0.25
MPV (fL)	7.99±1.63	7.31±1.14	**0.03***	8.26±1.62	7.94±1.60	0.38	7.89±1.49	7.71±1.37	0.56
RDW_CW(%)	12.10±1.07	11.84±0.86	0.24	12.18±1.36	11.81±0.84	0.19	12.86±2.87	12.02±0.98	0.17

Notes: CBZ: Carbamazepin; VPA: Valproate; LEV: Levetiracetam; WBC: White Blood Cell; HGB: Hemoglobin; HTC: Hematocrit; RDW_CW: Red Blood Cell Distribution Width Coefficent of Variation; PLT: Platelet; MPV: Mean Platelet Volume; NEU: Neutrophil; LYM: Lymphocyte; MONO: Monocyte; EOS: Eosinophil; BASO: Basophil; NLR: Neutrophil to Lymphocyte Ratio; PLR: Platelet to Lymphocyte Ratio; MLR: Monocyte to Lymphocyte Ratio; BLR: Basophil to Lymphocyte Ratio

Discussion

Platelet-lymphocyte ratio was found to be low in patients with epilepsy using AEDs (especially in VPA users) three months after drug use and this decrease supports the idea that AEDs such as VPA may cause hematological side effects. To the best of our knowledge, our study was the first to show the relationship between PLR and epilepsy patients receiving AED.

Many AEDs are associated with hematological disorders ranging from mild thrombocytopenia or neutropenia to anemia, from red cell aplasia to bone marrow failure. Fortunately, potentially lethal hematological disorders such as aplastic anemia are very rare (17,20). The pathogenetic mechanisms associated with antiepileptics are still unknown. They appear to be associated with an immunological mechanism, but pharmacokinetics and pharmacodynamic interactions of drugs may also play an important role (21). In addition to the known side effects, the negative effects of AEDs, especially VPA, on the mechanism of haemostasis were documented in some studies (22-24). Nevertheless, the mechanism of these adverse effects is not to be clearly elucidated yet. VPA's hematological side effects include dose-related thrombocytopenia, platelet dysfunction, and leukopenia (19,22,23). Valproate is one of the most commonly used drugs to induce thrombocytopenia (25).

In our study, statistically significant increase in neutropenia and thrombocytopenia were found in patients who used VPA compared to the control group and results support abovementioned studies.

Although the pharmacology and side effects of CBZ have been reviewed, a mechanism causing agranulocytosis has not been described (26). Carbamazepine was also reported to cause leukopenia, thrombocytopenia, agranulocytosis and aplastic anemia (20,27,28). In addition, CBZ has been shown to perform aplastic anemia, agranulocytosis, pancytopenia, mild anemia thrombocytopenia, leukopenia, and neutropenia (29). There were several cases that report rare side effects, such as blood dyscrasias. According to FDA Safety Information, reported hematological abnormalities include reduced erythrocytes, white cells and neutrophil counts, increased eosinophil counts, and agranulocytosis cases (30). CBZ-induced thrombocytopenia usually occurs two to four weeks after the start of treatment followed by a rapid improvement after prolonged application (31). Similar to the previous studies, thrombocytopenia was detected in patients receiving CBZ in our study.

Levetiracetam was reported to have hematological side effects such as neutropenia (6,32). Levetiracetam was demonstrated to induce anemia, leukopenia, neutropenia, and pancytopenia in various studies.

Jayendra R. Gohil and Tushar S. Agarwal reported a series of cases of pancytopenia with a large reduction in both neutrophil and platelet/ erythrocyte series associated with LEV usage (33). Although secondary pancytopenia is rare in LEV usage, it is still possible. A comprehensive literature review yielded a limited number of pancytopenia cases with the use of LEV (34). The specific mechanisms of action of LEV are not known, nevertheless, it is reasonable to assume that pancytopenia is associated with aplastic pancytopenia or bone marrow aplasia rather than microangiopathic hemolytic anemia or thrombotic thrombocytopenic purpura. These specific mechanisms of action were not found in case reports. Similar to case reports, lymphopenia, thrombocytopenia and monocyte deficiency were detected in patients receiving LEV in our study.

Conclusion

Easily obtained from whole blood count without any additional costs, NLR, MLR, PLR, and BLR values were not significantly different in epileptic patients on medical treatment in comparison to the control group in the present study.

Thus, although hematologic changes are rarely seen as a result of AED use, new findings are not different from the previous ones. However, hematological monitoring is suggested especially in the use of CBZ, VPA, and LEV. Further research is needed to evaluate the true pathogenetic mechanism based on hematological complications caused by antiepileptic drugs.

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Conflict of Interest: The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethical issues: All Authors declare, Originality and ethical approval of research. Responsibilities of research, responsibilities against local ethics commission are under the Authors responsibilities.

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Comparison of serum glutathione peroxidase levels in healthy controls and patients with oral cavity malignancy

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Abstract

Objective: In this study, we investigated the glutathione peroxidase enzyme activity changes in patients with oral cavity malignancies.

Material and Methods: Twenty-five patients with oral cavity malignancy and 24 healthy individuals were included in the study. There was no statistically significant difference between the groups in terms of age, gender and smoking-alcohol consumption habits.

Results: Glutathione peroxidase activity was found to be significantly lower in the blood of patients with oral cavity malignancies than the control group (2,238±0,039, p: 0,0001).

Conclusion: The level of glutathione peroxidase in the blood can be used as an important biomarker for the prognosis and to guide to the treatment approaches for the patients with oral cavity malignancy.

Keywords: Oral cavity malignancy, glutathione peroxidase, antioxidant enzyme

Introduction

Oral cavity malignancies are among the most common malignancies in the world and constitute approximately 8% of all malignancies (1). They are the most common subgroup of cancer in the head and neck region (except for non-melanoma skin cancer) (2). Oral squamous cell carcinoma is one of the most prevalent malignancies in the head and neck region and ranks sixth among all tumors worldwide (3). Despite advances in surgical techniques and treatment methods, the 5-year survival rate is quite low (1). Although the exact etiology is not clearly known, many factors such as smoking, alcohol consumption, tobacco chewing, poor oral hygiene and chronic irritation may play a role in the etiology (4). The primary approach for the treatment of oral cavity tumors includes surgical intervention. Adjuvant radiotherapy (RT) is used in the presence of risk factors after the primary surgery and in advanced stage disease; RT is used for definitive treatment when surgery is not possible in early stage disease. Chemotherapy (CT) may be added to the adjuvant RT in high risk cases (2).

Carcinogenesis is generally divided into three main stages: initiation, promotion, and progression. Reactive oxygen products and free radicals which may leads to hyper- and hypo- methylations of DNA are considered to play a role especially in the initiation and promotion stages (5).

Enzymes such as superoxide dismutase, catalase and glutathione peroxidase are involved in the protective mechanisms against free radicals. The production of reactive oxygen species (ROS) is an essential element of aerobic cellular metabolism. The imbalance between ROS production and antioxidant mechanism efficiency results in oxidative stress, leading to many diseases such as oral cavity malignancies (6).

Glutathione peroxidase (GPx) is a selenocysteine-dependent enzyme. GPx in cells is the most important hydrogen peroxide (H2O2) scavenging enzyme. This antioxidant enzyme catalyzes the reduction of H2O2 and leads to the oxidation of glutathione (GSH) which can be reduced by GSH reductase using NADPH (7, 8).

In this study, we compared the changes in serum glutathione peroxidase activity between the control group of healthy individuals and patients with oral cavity cancers.

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Material and Methods

In this study, the patients were selected from the patients who admitted to ENT clinic of Bagcilar Training and Research Hospital with a diagnosis of oral cavity squamous cell carcinoma. There was no other malignancy in the patient group except for oral cavity squamous cell carcinoma. Forty-nine people were included in the study. The patient group consisted of 25 (6 female, 19 male), the control group 24 individuals (8 females, 16 males, healthy individuals recruited from ENT outpatient clinic). Subjects aged between 28-85 years were included in the study. Smoking and alcohol habits, histopathological diagnosis of the patients were recorded from the patient follow-up data. A case report form was prepared for each individual. After informed consent, 5 ml venous blood samples were collected from each patient and each control. The blood was allowed to clot for 15 minutes and then centrifuged at 5.000 rpm for 10 minutes. Separated sera were stored at -80°C until analyzed.

Estimation of cytosolic GPx activity in hemolysate was based on the Paglia and Valentine method using hydrogen peroxide and the rate of disappearance of NADPH at 37°C and recorded spectrophotometrically (340 nm). The activity of the enzyme was presented as U/gHb.

Statistical Evaluation: In this study, statistical analysis was performed using NCSS (Number Cruncher Statistical System) 2007 Statistical Software (Utah, USA) package program.

In addition to descriptive statistical methods (mean, standard deviation), independent t-test was used for comparison of paired groups and chi-square test was used for the comparison of qualitative data. The results were evaluated at $p<0.05$ level.

Results

Twenty-five patients (19 males and 6 females) with oral cavity malignancy and 24 healthy controls (16 males, 6 females) were included in the study (table 1). The mean age was 55.8±13.4 years in the patient group and 54.5±11.91 years in the control group. No statistically significant difference was found in age and sex distributions between the control and patient groups (p= 0.722) (table2). No statistically significant difference was found between the control patient groups in terms of smoking distribution (p= 0.913) (table 2). There was no statistically significant difference between the control and patient groups in terms of alcohol consumption (p= 0.684) (table 2).

The glutathione peroxidase activity was 0.238±0.039 U/gHb in the patient group and 0.825±0.152 U/gHb in the control group. Glutathione peroxidase was significantly lower in the study group than the control group (p= 0.0001) (table 2).

Table 1: Types of oral cavity malignancy in the patient group

Pathology	Studied Group	
	n	%
SCC of the Floor of Mouth	4	16,00%
Lower Lip SCC	4	16,00%
Buccal Mucosal SCC	3	12,00%
SCC of the tongue	10	40,00%
Gingival SCC	1	4,00%
Hard Palate SCC	2	8,00%
Soft Palate SCC	1	4,00%

Table 2: Statistical data in patient and control groups

		Control Group n:24		Study Group n:25		P
Age		54,5±11,91		55,8±13,4		0,722*
Sex	**Male**	16	66,67%	19	76,00%	0,470+
	Female	8	33,33%	6	24,00%	
Smoking	**Yes**	9	37,50%	9	36,00%	0,913+
	No	15	62,50%	16	64,00%	
Alcohol Consumption	**Yes**	14	58,33%	16	64,00%	0,684+
	No	10	41,67%	9	36,00%	
Glutation Peroxidase		0,825±0,152		0,238±0,039		0,0001*

*** Independent t test + Chi-Square test**

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Discussion

It is believed that cancer cells exposes to much higher amount of ROS than normal cells and actively regulate multiple antioxidant systems to avoid the harmful effects of oxidative stress. Theoretically, overexpression of antioxidants may have an anticancerogenic effect in certain cancers by limiting the oxidants, but it can also lead to the survival of transformed cells by limiting apoptotic mechanisms in some cancers. In conclusion, the role of antioxidants in tumor formation and prognosis has been controversial for several years (7, 9). Therefore, we compared the levels of glutathione peroxidase in patients with oral cavity malignancy in the early stage with the levels in healthy control subjects and we examined the clinical implications of this in the literature.

Lee et al. found that glutathione peroxidase expression was higher in tissue samples of patients with oral squamous cell carcinoma and reported that this finding could be used as a useful biomarker in the survival and follow-up of recurrence in patients with Oral squamous cell carcinoma. (7). Banerjee et al. also found that mitochondrial glutathione peroxidase levels in tissue samples of patients with oral SCC were higher than healthy tissue samples. However, as the tumor stage increased, the enzyme level began to decrease. Therefore, they have recommended this enzyme activity assay as a biomarker that can be used in the follow-up of tumor progression and in selecting treatment modalities (10). In our study, serum glutathione peroxidase activity was significantly lower in patients with oral SCC than in healthy control subjects at the initial diagnosis stage independent of the tumor stage. This suggests that the enzyme activity can be used as a biomarker to assist in the diagnosis of malignancy and prognosis.

In a study conducted by Fu et al. in 2016, glutathione peroxidase levels were found to be higher in tissue samples of patients with oral SCC compared to the patients with verrucous carcinoma. Therefore, they suggested that in contrast to verrucous carcinoma, distant metastasis and local spread were more frequent in cases with oral SCC (11). Furthermore, in many cases of pathology, distinction between verrucous carcinoma and early stage oral SCC may be difficult. The determination of enzyme activity appears to be a useful biomarker in the diagnosis of more aggressive oral SCC cases and in preventing the selection of over-treatment modalities in verrucous carcinoma. Fu et al. found that in 2010, glutathione peroxidase levels were higher in patients with buccal mucosal SCC. This enzyme activity has been found to be higher in patients who had a better survival (5).

Malinowska et al. suggested that increasing the activity of glutathione peroxidase by using copper (II) complex can be used to create an anticancer treatment protocol (6). In the light of these results, it can be interpreted that, determination of the enzyme activity initially and the activity enhancing preparations added to the treatment protocol by selecting the appropriate patient population may be effective in improving patient survival.

Balasenthil et al. have observed that glutathione peroxidase activity increases in oral carcinoma tissue samples that they have experimentally formed in hamsters compared to normal tissues. This was interpreted as the increase in this enzyme activity might play a role in carcinogenesis (12). These studies are very helpful in selecting treatment modality and provide a better understanding of carcinogenesis.

Among the study groups of Gurudath et al., which included oral squamous fibrosis, oral leukoplakia and oral cancer patients, oral cancer group showed the lowest GPx levels (8). Low glutathione peroxidase levels indicate that many cancer cells cannot detoxify hydrogen peroxide. (13) These results are consistent with our study.

Significant evidence indicates that antioxidant enzymes prevent both initiation and promotion of cancerogenesis. In the literature, the low activity of these enzymes has been interpreted as playing a key role in the progression of the lesion (8).

Conclusion

As a result, antioxidant enzyme levels are an interesting research topic that has a potential role in cancerogenesis and is the basis of the cellular antioxidant defense mechanism. Therefore, glutathione peroxidase may be a potential biochemical marker to assess the disease process. This study evaluates the change in enzyme level in healthy patients. This antioxidant enzyme may also serve as a guide for therapeutic targets and prognosis in patients suffering from such a disease. We believe that the role of antioxidant mechanisms in cancerogenesis, diagnosis and treatment methods and prevention of cancerogenesis in the future is an area that should be considered and investigated. However, further detailed biochemical and histopathological studies are needed to determine the actual role of biochemical parameters in various clinical stages.

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.

Informed consent form: Informed consent was obtained from all individual participants included in the study.

Acknowledgement: Approval of Bagcilar Training and Research Hospital Clinical Research Ethics Committee was obtained for this non-randomized prospective clinical laboratory study (2019.03.1.01.020).

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Ethical issues: All Authors declare, originality and ethical approval of research. Responsibilities of research, responsibilities against local ethics commission are under the Authors responsibilities.

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The novel translocation of t (1;21) in multiple myeloma with poor prognosis

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Abstract

Objective: Multiple myeloma (MM) is characterized as the neoplastic proliferation of plasma cells producing a monoclonal paraprotein. The aim of this paper is to report complex karyotype that leads to a fatal clinical course in a patient with MM.

Case: A 48-year-old male patient was diagnosed as MM free lambda. The karyotype of the patient was 46, XY, t(1;21) (p11;p11), del(3) (q25;q29), del(6) (q24;q26), t(11;14) (q13;q32), del(13) (q14;q21) in cytogenetic evaluation. Vincristine, doxorubicin and dexamethasone were started. The creatinine levels increased after the second course of chemotherapy, the chemotherapy protocol was switched to bortezomib and dexamethasone. Patient was admitted to the emergency department with pneumonia after the second chemotherapy cycle. Despite using broad spectrum antibiotics and oxygen support, he died after the development of sepsis syndrome.

Conclusion: The anomaly of t (1;21) (p11;p11), that we detected in this case was detected in a case with MM for the first time and this anomaly has not been detected between these breaking points in any malignancies before. Although the prognostic impact of this unique anomaly may be unclear, further studies are needed to evaluate the effect of cytogenetic anomalies on prognosis of multiple myeloma.

Keywords: multiple myeloma, karyotyping, chromosome aberrations

Introduction

Multiple myeloma (MM) is characterized as the neoplastic proliferation of plasma cells producing a monoclonal paraprotein (1, 2). Multiple myeloma is a heterogeneous disease with overall survival less than 1 year or more than 10 years. The staging, patient factors, disease biology and response to therapy are the factors affecting prognosis (1). The cytogenetic anomalies of patients have prognostic significance. In studies, it was stated that cytogenetic abnormalities were very important in the diagnosis and follow-up (3). According to high-risk and standard-risk cytogenetic abnormalities, response to treatment and resistance can be estimated (4, 5). There are numerous cytogenetic abnormalities in the literature (6, 7). The aim of this paper is to report a new translocation with complex karyotype in a patient with MM.

Case report

A 48-year-old male patient was admitted to our emergency department with the symptom of black stool. The hemoglobin value was 7.3 g/dl, platelet count was 37×103/µl and leukocyte count was normal at admission. The patient was consulted to hematology department due to the presence of bicytopenia, high creatinine level and hypercalcemia. Monoclonal free lambda band was observed in the serum immunofixation electrophoresis. The serum free lambda level was 13,050 mg/l. His serum calcium level was 15 mg/dl. The patient was hospitalized. Bone marrow biopsy showed diffuse neoplastic plasma cell infiltration.

The bone marrow sample of the patient was cultured for 24 hours and then GTG (Giemsa-Trypsin) banding was performed. Twenty metaphases of the patient were analyzed and karyotype was generated according to the 2013 International System for Human Cytogenetic Nomenclature (ISCN) (8). Complex karyotype was detected in all of 20 metaphases. The karyotype of the patient was 46, XY, t(1;21) (p11;p11), del(3) (q25;q29), del(6) (q24;q26), t(11;14) (q13;q32), del(13) (q14;q21). Translocations between chromosomes 1 and 21, deletions in the long arms of chromosomes 6 and 13 and translocations between chromosomes 11 and 14 were identified in all analyzed metaphases (Figure 1).

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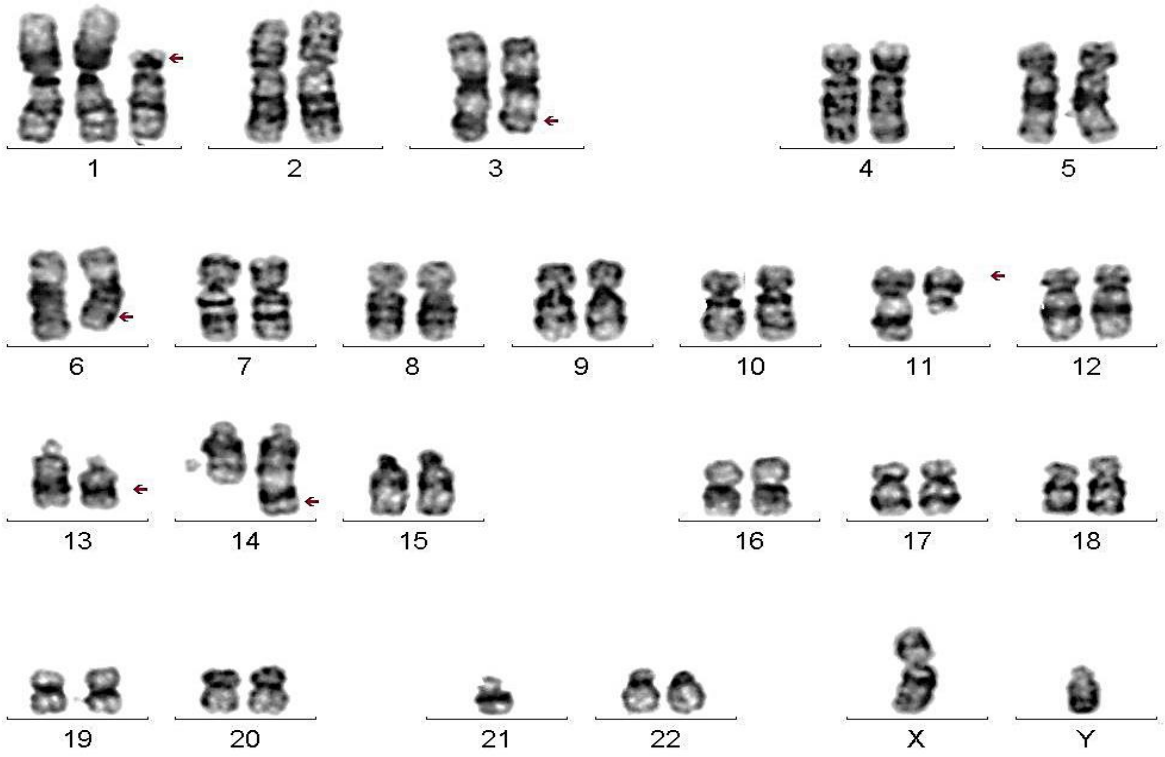

Figure 1. Karyotype of the patient (G-banding with Giemsa-Trypsin 358x316 mm (72 x 72 DPI)).

The patient was diagnosed with MM and the treatment of vincristine, doxorubicin, dexamethasone (vincristine 0.4 mg/day on day 1, 2, 3, 4, intravenously, doxorubicin 9 mg/m2 on day 1, 2, 3, 4, intravenously, dexamethasone 40 mg/day on day 1-4, 9-12 and 17-20, peroral) was initiated. A minimal decrease was observed in the creatinine levels during follow-up in first chemotherapy cycle. When the creatinine levels increased again after the second course of chemotherapy, hemodialysis was initiated. The chemotherapy protocol was switched to bortezomib and dexamethasone (bortezomib 1.3 mg/m2/day on day 1, 4, 8, 11, subcutaneous and dexamethasone 40 mg/day on days 1-4, 9-12, peroral). After 4 cycles, autologous stem cell transplantation was planned. After the second chemotherapy cycle, the patient was admitted to the emergency department with the complaints of coughing and producing sputum. He was diagnosed as pneumonia. He was hospitalized again and moxifloxacin was started. After 2 days, the oxygen saturation level decreased. Creatinine levels showed progressive elevation. Despite the broad spectrum antibiotics and oxygen support, he died because of sepsis syndrome. The patient's informed consent form was obtained according to local ethic commission rules.

Discussion

New treatment modalities have become available for the patients with MM (9). Several cytogenetic abnormalities [t(4;14), del(17/17p), t(14;16), t(14;20), nonhyperdiploidy, gain(1q)] were associated with poor prognosis. Treatment recommendations were different in high-risk and standard risk MM (9). In this case, we reported a new translocation of t(1;21) (p11;p11), which did not occur between these points previously according to the databases that we have searched (Atlas of Genetics and Cytogenetics in Oncology and Hematology and Mitelman Database of Chromosome Aberrations and Gene Fusions in Cancer). When we evaluated the other anomalies of the patient, we saw that t(11;14) (q13;q32) is one of the most common translocations of MM (9). Translocation t(11;14) was identified as neutral in some studies or favorable in other studies (9). When t(11;14) (q13;q32) was included in the complex karyotype, del(3)(q) and the anomalies of chromosome 1 can be detected together (10, 11). Also in our case, t(11;14) (q13;q32) was accompanied by both del(13) (q14;q21) and dic(1;21) (p11;p11) that we reported as a new translocation. The anomaly of del (3)(q) is associated with short overall survival. The other anomaly was detected in our patient which was del (6)(q) occurs in 2-5% of MM patients (12-14).

This anomaly indicates a favorable prognosis in adult acute lymphoblastic leukemia. The same deletion is associated poor prognosis in MM (15). In the literature, it was also reported another rare cytogenetic abnormality t(3;16) (q21; q22) which detected in MM, associated with poor prognosis (16).

Conclusion

The anomaly of t(1;21) (p11;p11) is a new entity which has not been detected between these breaking points in any malignancies before. It was detected in a case with MM for the first time. Although, the prognostic impact of this unique anomaly may be unclear. Since the complex karyotype was detected in this patient, it was difficult to say t(1;21) (p11;p11) is associated with poor prognosis.

Further studies are needed to evaluate the effect of cytogenetic anomalies on prognosis of multiple myeloma.

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Ethical issues: All Authors declare, originality and ethical approval of research. Responsibilities of research, responsibilities against local ethics commission are under the Authors responsibilities.

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Anesthesia management in a patient with zellweger syndrome

Gökhan Kılınç[1]*

Abstract

Objective: Zellweger syndrome (ZS) is an autosomal recessive disorder in the spectrum of peroxisome biogenesis disorders including punctate and is defined as cerebrohepatorenal syndrome due to multiple congenital anomalies including brain, liver and kidneys. We wanted to draw attention to this issue by sharing our anesthetic experiences in a child with Zellweger syndrome.

Case: Appendectomy was planned by pediatric surgery in a 4 year old and 16 kg male patient who was diagnosed as Zellweger syndrome. Physical examination revealed large forehead, large tongue, small chinhypotony, mental motor retardation, and hepatosplenomegaly. Following the introduction of routine monitors, anesthesia were induced intravenously and maintained with sevoflurane in an 50% oxygen- 50% air mixture. The patient was intubated and ventilated with a safe pressure control mode. The patient was hemodynamically stable during surgery. After spontaneous breathing of the patient, extubation was applied smoothly.

Conclusion: Zellweger syndrome includes alarming features for the anesthesiologist. Before any procedure, the pulmonary condition should be carefully evaluated. Hepatic dysfunction may lead to a change in the metabolism of drugs based on hypoalbuminemia, coagulopathy and liver pathways. Since liver dysfunction may lead to coagulopathy, caution should be exercised when applying regional anesthesia techniques.

Keywords: Zellweger syndrome, anesthesia, appendectomy

Introduction

Zellweger syndrome (ZS), neonatal adrenoleukodystrophy (ALD), infantile refsum disease (IRD) and rhizomelic chondrodysplasia punctata (RCP) peroxisome biogenesis disorders in the spectrum of autosomal recessive disease is an autosomal recession and generalized with impairment of peroxisomal functions. This syndrome is also referred to as cerebrohepatorenal syndrome due to multiple congenital anomalies involving the brain, liver and kidneys. Facial dysmorphism, neonatal hypotonia, poor nutrition, neurocognitive delay and seizures, hepatomegaly and renal cysts are the main features of this disease. Life expectancy is approximately 6 months (1).

Peroxisomes are organelles which are found in all body cells except mature erythrocytes and especially myelin, and their main function is the biosynthesis of plasmogenic pathways in the pathway of fatty acids metabolism. Zellweger Syndrome (ZS), the prototype and the most serious of peroxisomal defects, is a very rare disease with autosomal recessive inheritance. The genetic defect in Zellweger Syndrome arises from the mutation of the PXR1 gene located on chromosome 12 and first described by Hans Zellweger (2).

We aimed to contribute to the literature by presenting the anesthesia approach during appendectomy in a 4 year old patient with ZS.

Case

Appendectomy was planned for acute appendicitis by pediatric surgery in a 4 year old and 16 kg male patient who was diagnosed as Zellweger syndrome. Physical examination revealed large forehead, large tongue, small chinhypotony, mental motor retardation, and hepatosplenomegaly. Hb: 12.1 gr/dl, aspartate aminotransferase: 22 U/l, alanine aminotransferase : 9 U/l were found in the patient who did not have any problems of bleeding clotting system. The patient was diagnosed with epilepsy and used valproic acid for treatment. The patient who had a fasting period of 6 hours before the anesthesia application was taken to the operating room.

Saturation (SpO2), heart rate (CAD) by electrocardiography, and non-invasive blood pressure (BP) measurement was conducted.

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Following the introduction of routine monitors, a 24G intravenous cannula was inserted at the left brachial vein, anesthesia, midazolam 1mg, propofol 2 mg/kg and remifentanil at 0.25 mcg/kg/min and rocuronium bromide 0,5mg/kg were induced intravenously and maintained with sevoflurane in an 50% oxygen- 50% air mixture. The patient was intubated with endotracheal tube No. 5 and ventilated with a safe pressure control mode. The patient was delivered to the surgical team and the operation started. The patient was hemodynamically stable during surgery. After spontaneous breathing of the patient, sugammadex 2 mg/kg was administered for reversing the neuromuscular blockade at the end of the procedure and extubation was applied smoothly. The patient was sent for follow-up to the pediatric intensive care unit as planned.

Informed consent was obtained from the patient's family for being included in the study.

Discussion

ZS is a serious disease with multiple congenital anomalies which are progressive and fatal. While the affected children can live only 2-3 months, there are reports of patients living up to 2 years with more care and genetic-phenotypic variability. Patients with ZS typically die from apnea, respiratory failure or infection complications (3). Our patient was the first 4 years old patient in the literature.

Zellweger syndrome includes alarming features for the anesthesiologist. Before any procedure, the pulmonary condition should be carefully evaluated. Sedation is not recommended because it may increase the respiratory failure due to hypotonia. It is not recommended to use succinylcholine as a muscle relaxant due to the risk of possible hyperkalemia in children with ZS and nondepolarizing muscle relaxants should be used with caution because of hypotonia present in patients with ZS (4). Hepatic dysfunction in patients with Zellweger syndrome may lead to a change in the metabolism of drugs based on hypoalbuminemia, coagulopathy and liver pathways. Chronic use of anticonvulsant drugs may also alter liver function (5). Since liver dysfunction may lead to coagulopathy, caution should be exercised when applying regional anesthesia techniques. The use of anesthetic agents that reduce the seizure threshold should also be avoided. Because of the use of anticonvulsant medication due to epilepsy in our patient, liver function tests and coagulation tests were carefully examined and found to be normal.

Renal functions of these patients may also be impaired. Stress response may be insufficient in these patients, and some patients may require steroid administration in the perioperative period. Antibiotic prophylaxis is required for children with congenital heart disease. Joint contractures in patients with Zellweger syndrome may complicate venous cannulation. It may be difficult to give intraoperative position to the patients and protective pad applications may be required (6).

Conclusion

As a result, ZS is a short-lived, progressive, complex disease that affects many organs. Since children with ZS have respiratory problems, hepatic dysfunction, gastro-oesophageal reflux, epileptic seizures and severe hypotonia, anesthesia planning and management should focus on these points.

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Author's Contributions: **G.K,** were contributed to planning the research, patient examination, preparation of the article.

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