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Original Article

Retrospective evaluation of patients hospitalized due to bronchial asthma during 1991-1995 at Dr. Sami Ulus Center for Pediatrics

1991-1995 yıllarında Dr. Sami Ulus Çocuk Sağlığı ve Hastalıkları Merkezi'ne yatan bronşial astımlı hastaların retrospektif değerlendirilmesi

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ABSTRACT

Introduction: Asthma is a heterogeneous disease characterized by chronic airway inflammation. Bronchial asthma is the most common chronic disease of childhood and is among the causes of frequent hospitalization in children. This study aims to describe the demographic and clinical characteristics of the patients hospitalized due to "bronchial asthma" within five years.

Methods: The hospital records of patients aged 0-15 years admitted with the diagnosis of bronchial asthma to the Dr. Sami Ulus Center for Pediatrics between 1991-1995 were examined. The sociodemographic characteristics, skin, and laboratory values of the patients and the medications they received were examined.

Results: Of the total 135 patients, 58.5% (n = 79) were males. The age distribution of the inpatients was mostly in the age group of 3-5 years (57.8%, n = 78). The mean annual hospitalization rate was 0.53%. Patients hospitalized for five days composed the largest group (39.3%, n = 53). Most of the hospitalized patients (74.1%; n = 100) were coming from urban settings. The most common pathologic condition on chest X-ray were increased aeration + infiltration (52%, n = 70). Sinusitis was accompanied to 78.5% of the hospitalizations. There was 50.4% (n = 68) leukocytosis in the hemograms. Most sensitive skin tests were mixed grass pollen and house dust. The primary medication used in prophylactic treatments was Ketotifen. Salbutamol was the most common medication used in the emergency department, theophylline and antibiotics for the bedside, and salbutamol syrup was the most prescribed medication for the discharged patients.

Conclusion: The greater proportion of male gender and 3-5 year-olds in the study group indicated that these risk factors were consistent with the previous literature. The similarity of annual admission rates within the years indicates that there is no change in asthma frequency in the population served over time. Even though the number of cases requiring antibiotics in bronchial asthma is high (similar to sinusitis), we believe that the use of antibiotics should be lowered.

Keywords: Child, asthma, epidemiology, antibiotics, atopy

ÖZ

Giriş: Astım, genellikle kronik hava yolu inflamasyonu ile karakterize heterojen bir hastalıktır. Bronşiyal astım çocukluk çağının en yaygın kronik hastalığıdır ve çocukların hastaneye sık yatış nedenleri arasındadır. Bu çalışma ile 5 yıllık bir süre içerisinde"Bronşiyal astım" tanısıyla hastaneye yatan hastaların demografik ve klinik özelliklerinin tanımlanarak değerlendirilmesi amaçlanmıştır.

Yöntem: Doktor Sami Ulus Çocuk Hastalıkları Merkezine, 1991-1995 yıllan arasında, Bronşiyal astım tanısıyla yatırılan 0-15 yaş arası hastaların kayıtları incelendi. Hastaların sosyodemografik özellikleri, deri ve laboratuvar değerleri ve aldıkları ilaç tedavileri incelendi.

Bulgular: Toplam 135 hastanın %58,5'i (n=79) erkekti. Hastaneye yatış yapılan hastalarda yaş dağılımı en çok %57,8 (n=78) ile 3-5 yaş grubuna aitti. Ortalama yıllık yatış oranı. %5,3 bulundu. Beş gün ve üzeri yatan hastalar en büyük grubu oluşturuyordu (%39,3; n=53). Yatan hastaların çoğu (%74,1; n=100) kentsel yerleşimliydi. Akciğer grafilerinde en sık görülen patolojik durum havalanma artışı + infiltrasyonun bir arada olduğu durumdu (%52; n=70). Sinüzit %78,5 oranda yatışlara eşlik ediyordu. Hemogramda %50,4 (n=68) lökositoz vardı. En çok duyarlı deri testleri, karma çayır polenleri ve ev tozuydu. Profilaktik tedavide öncelikle ketotifen kullanılıyordu. Acil serviste en fazla salbutamol, serviste teofilin ve antibiyotik; taburcu edilen hastalarda ise en fazla salbutamol şurup reçete edilmekteydi.

Sonuç: Araştırma grubunda erkek cinsiyetin ve 3-5 yaş grubunun daha fazla olması, bunların önceki literatürle uyumlu risk faktörleri olduğunu göstermiştir. Yıllık yatış oranlarının yıllara göre benzer olması, hastanenin hizmet verdiği popülasyonda astım sıklığında zamanla bir değişiklik olmadığını göstermektedir. Bronşiyal astımda sinüzit gibi antibiyotik kullanımını gerektiren durumlar fazla olmakla birlikte, yine de antibiyotik kullanım oranını düşürülmesi gerektiğine inanıyoruz.

Anahtar Kelimeler: Çocuk, astım, epidemiyoloji, antibiyotik, atopi

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Introduction

Asthma is a heterogeneous disease characterized by chronic airway inflammation. It is defined by a history of symptoms such as variable expiratory flow restriction, wheezing, shortness of breath, chest compressions and cough, which may change in frequency and extent over time [1]. Asthma is the most common chronic disease of childhood and is the leading cause of childhood morbidity due to chronic illnesses measured by loss of school days, emergency room visits, and hospital admission [2,3]. The distribution of the disease varies between 1% and 18% between countries and between regions within countries [2,4–6]. Asthma can occur at any age, but the highest incidence is at childhood. More than half of patients with bronchial asthma (B. asthma) are reported to have symptoms starting in childhood [7]. In a study conducted with children in Turkey, the cumulative prevalence of asthma was reported as 14.7% and the prevalence of asthma in the 12-month age group as 2.8% [8].

Asthma starts in males earlier than in females [9–11]. The majority of asthmatic children over three years of age have atopy, and atopy is one of the most important risk factors for asthma development [12]. Nevertheless, no intervention has been shown to prevent the development of asthma or alter its long-term natural course [1].

Some viral infections (respiratory syncytial virus and rhinovirus) are associated with recurrent wheezing in childhood. However, wheezing in this age group is highly heterogeneous, and wheezing per se in this age group does not necessarily indicate asthma. In addition, many young children may wheeze during viral infections. Therefore, it is difficult to evaluate respiratory tract infections and wheezing as an initial or recurrent clinical presentation of childhood asthma [10,13].

This study aimed to describe the demographic and clinical characteristics of patients with asthma in a 5-year period.

Methods

This study examined the records of patients aged 0-15 years who were admitted to the Dr. Sami Ulus Center for Pediatrics, between 1991 and 1995 with a diagnosis of B. asthma.

From the examined records of patients; age, gender, duration of hospitalization, the status of prophylactic treatment before admission, factors predisposing to admission, region and socioeconomic status of the patient, skin test results, emergency and in-patient treatment, outpatient management, history of atopy, and used medications were recorded.

Statistical analysis

Analyzes of the study were done with the SPSS for Windows v.5.01. The data are presented in numbers and percentages.

Results

Between 1991 and 1995, 135 children aged 0-15 years were hospitalized and treated due to B. asthma attack in the Dr. Sami Ulus Center for Pediatrics.

Table 1 summarizes the distribution of sex, age groups, number of hospitalized days, place of residence, and health insurance according to years of the children with asthma in the period between 1991-1995 at the Dr. Sami Ulus Center for Pediatrics. Patients aged 3-5 years (57.8%,n = 56) were more than the other age groups.Of the patients, 58.5% (n=79) were boys, while 41.5% (n=56) were girls. The number of days of hospitalization ranged from 1 day (5.9%, n=8)to 5 days (39.3%, n=53). Patients from urban settlements constituted 74.1% (n = 100). The majority of patients (40%) had green card health insurance.

Table 2 shows hospitalization rates of asthmatic children for every 1000 hospitalized patients. Accordingly, the average annual asthma incidence per year between 1991 and 1995 was calculated as 5.3.

The proportion of those with atopy in their family was 35.5%. Thirty-nine of the patients with atopy in the family had B. asthma, five had allergic rhinitis, and seven had eczema.

Table 3 shows the evaluation of the laboratory results of the asthmatic patients. Pulmonary functions were normal in 52.0% (n = 14), while pathologic in the remaining patients. The most common pathologic condition was a combination of increased aeration + infiltration (52%, n = 70). Water's X-ray was found to be abnormal (significant aeration loss and/or mucosal thickening) in 78.5% of cases (n = 44). Sweat test, PPD, and electrolytes were within normal limits. 50.4% (n = 68) of the hemograms demonstrated leukocytosis with peripheral smears showing left shift in 44.0% (n = 59) and eosinophilia in 3.5% (n = 5). Eosinophilia was present in 67% (n = 14) of the nasal smears examined. High IgE was observed in 27.0% (n = 27) of the patients.

Table 1. Distribution of sex, age groups, number of hospitalized days, place of residence and health-care providers according to years (n = 135) in asthmatic children hospitalized between 1991-1995 at the Dr. Sami Ulus Center for Pediatrics.

	1991		1992		1993		1994		1995		Total	
	n	%	n	%	n	%	n	%	n	%	n	%
Sex												
Male	12	57.1	21	58.3	17	65.4	15	50.0	14	63.6	79	58.5
Female	9	42.9	15	41.7	9	34.6	15	50.0	8	36.4	56	41.5
Age groups												
0-2	3	14.3	12	33.3	6	23.1	10	33.3	8	36.4	39	28.9
3-5	15	71.4	20	55.6	18	69.2	15	50.0	10	45.5	78	57.8
6-15	3	14.3	4	11.1	2	7.7	5	16.7	4	18.1	18	13.3
Days hospitalized												
1	1	4.8	5	13.9	1	3.8	0	0.0	1	4.5	8	5.9
2	6	28.6	5	13.9	4	15.4	0	0.0	1	4.5	16	11.9
3	6	28.6	12	33.3	10	38.5	5	16.7	5	22.8	38	28.1
4	4	19.0	6	16.7	3	11.5	6	20.0	1	4.5	20	14.8
5 and more	4	19.0	8	22.2	8	30.8	19	63.3	14	63.7	53	39.3
Settlement												
Urban	14	66.7	25	69.4	20	76.9	24	80.0	17	77.3	100	74.1
Rural	7	33.3	11	30.6	6	23.1	6	20.0	5	22.7	35	25.9
Health coverage												
Self	11	52.4	6	16.7	8	30.8	14	46.7	7	31.8	46	34.1
Insured	6	28.6	10	27.7	7	26.9	7	23.3	5	22.7	35	25.9
Green card	4	19.0	20	55.6	11	42.3	9	30.0	10	45.5	54	40.0

Values represent column percentages.

Table 2. Admission rates of children aged between 0 and 15 years at the Dr.Sami Ulus Center for Pediatrics

Years	Number of total admissions	Number of asthma cases	Ratio (/thousand)
1991	4687	21	4.5
1992	5274	36	6.8
1993	5049	26	5.1
1994	5110	30	5.9
1995	5229	22	4.1
Total	25347	135	5.3

Table 3. Evaluation of laboratory results of asthmatic patients hospitalized between the years 1991-1995 at the Dr. Sami Ulus Center for Pediatrics.

			n	%
Chest X-ray	Increased aeration + infiltration		70	52.0
	Only increased aeration		50	37.0
	Atelectasis		1	0.7
	Normal		14	10.3
Water's graph	Abnormal		44	78.5
	Normal		12	21.5
Electrolytes	Abnormal		0	0.0
	Normal		135	100.0
Hemogram	Leucocyte	Normal	67	49.6
		Abnormal(Leukocytosis)	68	50.4
	Hemoglobin	Normal	123	91.0
		Düşük	12	9.0
	Peripheral smear	Normal	65	48.0
		Left shift	59	44.0
		Eosinophilia	5	3.5
		Lymphocytosis	6	4.5
Nasal smear	Eosinophil (+)		14	67.0
	Eosinophil (-)		7	33.0
Sweat test	Abnormal		0	0.0
	Normal		36	100.0
PPD	Abnormal		0	0.0
	Normal		58	100.0
IgE	Normal		46	73.0
	High		17	27.0

The first three skin tests in patients with bronchial asthma withthe highest positivity were tree pollen mixture (58%, n = 11), house dust mix (56%, n = 18), and animal hair(53%, n = 17) (Table 4).

Table 4. Assessment of skin tests seen in asthmatic children between 1991-1995 at the Dr. Sami Ulus Center forPediatrics

	Negative		Positive		
Skin tests	**n**	**%**	**n**	**%**	**Total**
Wool	7	53.8	6	46.2	13
Grass	18	47.4	20	52.6	38
Wood	8	42.1	11	57.9	19
House dust	14	43.8	18	56.2	32
Mushroom	7	50.0	7	50.0	14
Milk	22	50.0	22	50.0	44
Dermatophagoides	13	54.2	11	45.8	24
Animal hair	8	47.1	9	52.9	17
Other	21	53.8	18	46.2	39

Table 5 shows the treatment of asthmatic children with various conditions. 29.3% (n = 40) of the asthmatic patients received prophylactic treatment before hospitalization. Distribution of the prophylactic medications were as follows: 29 ketotifen, 6 Na-chromoglycate, 4 steroid inhalers and 1 immunotherapy. The most common medications applied in the emergency department were salbutamol (puff or nebulizer) (52%; n = 71) and adrenaline (36%; n = 49). Inpatients received most commonly theophylline (cofilin) syrup (92.6%; n = 125), antibiotics (85.0%, n = 115), aminophylline (66.6%; n = 90), and salbutamol (61.5%, n = 83) in the form of nebulizer or inhaler. The patients were discharged from the hospital most commonly on salbutamol syrup (85%, n = 115), theophylline syrup (74%; n = 100), and sodium cromoglycate (4.4%; n=6).

Table 5. Medications of the asthmatic patients in different settings (n=135)

Type of medication		n	%
Prophylactic	**Received**	40	29.3
	Ketotifen	29	
	Na-Cromoglycate	6	
	Steroid (inhaler)	4	
	Immunotherapy	1	
	Did not receive	95	70.7
Emergency ward	Adrenaline	49	36.0
	Steroid (IVP,2 mg/kg)	34	29.0
	Salbutamol	71	52.0
	Aminophylline(IVP)	15	11.0
Inpatient wards	Aminophylline (Infusion)	90	66.6
	Steroid (IVP)	45	33.0
	Steroid (oral)	17	12.6
	Salbutamol (nebulizer, puff, or inhaler)	83	61.5
	Salbutamol (syrup)	25	18.5
	Theophylline (cofilin) syrup	125	92.6
	Antibiotics	115	85.0
Discharge	Steroid tabletsor inhaler	14	10.4
	Ketotifen syrup	37	27.0
	Salbutamol syrup	115	85.0
	Theophyllinesyrup (cofilin)	100	74.0
	Na-Cromoglycate	6	4.4
	Antibiotics	97	72.0

IVP: Intravenous perfusion.

Children with asthma included in this study were invited for control in the allergy policlinics within 7-10 days after being discharged from the hospital. Of the patients, 67% (n = 90) came to the control and had their follow-up.

Discussion

In this study, the health records of children who were hospitalized were investigated in a period of five years, and descriptive statistics of the patients' socio-demographic, laboratory and medication records were analyzed to support the hypothesis about the etiology of the disease and/or to contribute to new hypotheses.

In this study, the percentage of male gender of asthmatic patients was higher than that of females. In a study conducted in the Portland area from 1966 to 1987, 0 to 4 age group was the most common age among 0 to 14-year-old children with asthma. Males constituted 70% of the 0-4-year-old patients, while the proportion of males among the 5-14-year-old decreased to 62%, and finally equalized with the girls during adolescence [14]. Again in a hospital-based study in 2012, the male gender ratio among asthmatic children aged 7-14 years was reported as 67%[15]. Childhood asthma is more common among boys. This is because the respiratory tract in men is narrower and has higher tonus, which can easily cause

difficulties in the airflow due to various effects. Since the difference in diameter equalizes between sexes after age 10, so does the prevalence of the disease [3]. Our results are consistent with these studies.

In our study, the five-year average hospitalization rate of children with asthma was found at 5.3%. This rate increased from 7.1% in 1969 to 13.5% in 1982 in New Zealand. Between 1974 and 1983 in Canada, there was a two-fold increase[16,17]. In the study conducted by Burt Gerstman and colleagues, the rate of childhood asthma among children aged 5-14 years increased from 2.3% in 1980 to 4.5% in 1984 but decreased during the following years. While the prevalence was 2.2% in 1980 among the 10-14 years aged, this ratio increased to 3.2% in 1984 and became 3% in 1986 [18]. In a study conducted in Boston in 1992, the hospitalization rate for asthmatic children was reported as 4.2% [19].
While significant increases in asthma hospitalization have been reported in many countries, there was no such increase during our study period. Most of the asthmatic patients hospitalized in our hospital were generally severely ill, and they were residing in the low socioeconomic areas of the city. Having received not many light cases may be due to the availability and easy access to the many private clinics in the area, who were dealing mainly with light cases. As a matter of fact, a similar reduction in hospitalization has been reported in a study in Finland as a result of private outpatient clinics, especially providing nebulizer treatment[20].

More than half of the patients in this study were between the ages of 3-5 years. We find it noteworthy to think about the reasons of this change over the years. The risk group for each year is age 3-5. Several studies have reported that B. asthma symptoms start in the majority of patients before age five[21]. The rate of hospitalization among asthmatic children in the community is particularly high in the 0-5 age group [16,22]. Our findings are consistent with other studies in this area.

Asthmatic children who were admitted to our hospital for more than five days constitute the largest group with 39.3%. A study of asthmatic children in the Portland area between 1966 and 1987 showed that hospital stay was as follows: 1 day 82%, 2-3 days 7.4%, five days 6%, and more than six days 5% [14]. Since most of the inpatients were not well-trained and educated, the length of the hospitalization can be regarded as an opportunity to provide both the necessary training and do the necessary examinations. When compared, the duration of hospitalization of our patients is longer than others reported in the literature.

More than two-thirds of patients with bronchial asthma were located in urban areas. There are differences in asthma prevalence between urban and rural areas according to different studies [23–25]. Breastfeeding is longer in the rural area; in this way, the risk of developing a cow's milk allergy is reduced. In urban life, environmental pollution, warming, and fuels of motor vehicles, and house dust mites allergens increase the risk of asthma [3]. In America, asthma rates are higher in urban areas. This is attributed to the large black population living in urban settings. There is also an increase in admissions because the health care system cannot provide the necessary care and education [18].

In other studies, asthma prevalence was found to be low in children who were raised in high-income families and high among children of families earning below the poverty line. Weitzmann et al. reported that asthma rates were higher in poor and black children who were primarily dependent on social and economic support [22,26]. The majority of the cases coming from urban and suburban settlements are consistent with the above-mentioned general findings.

About half of the patients with asthma who were hospitalized were green card owners. Thus, we can claim that most of the patients included in this study constitute patients from the low-income community. As mentioned in many studies, asthma prevalence and hospitalization rates are higher in the low-income segments [18,22,26].

Many patients had a family history of atopy. An important clue in the diagnosis of B. asthma is the presence of other allergy-related diseases such as asthma, allergic eyes, hay fever, or eczema in the family. Many authors have reported familial atopy as more than 50%. There is no doubt about genetic susceptibility. However, predisposition does not always lead to the disease;different grades of severity and different clinical pictures may appear in the genealogy [3,27,28].

Since the infiltrative appearance of bronchial asthma may be related to small atelectatic areas due to mucus plugs, it is more appropriate not to start antibiotics in the absence of leukocytosis, leftshift, and sinusitis. The use of antibiotics in our study patients was usually limited to such patients. Besides, chest X-ray routines may not be required in each attack if there is no obvious pathology in patients with prior follow-up and available chest X-ray. The second important issue is the high prevalence of abnormal sinus findings. Compatible with the literature, sinusitis adversely affects asthma [29]. IgE and nasal smears are not discriminant but merely supportive indicators.

Allergens that mostlydisturb allergic asthmatics are house dust mites. These are small creaturesresembling cockroaches or heater bugs, which are not seeable by the naked eye. Approximately 60% of allergic asthmatics in Turkey are sensitive to insects. The most common types of these creatures are Dermatophagoides pteronyssinus (Dpt) and Dermatophagoides farinea (Df). The most common type in Turkey is Dpt [3].

In the study of Arslan et al. [30], house dust (31.7%), mixed grass (2.2%), wood (4.8%) and cat hair (2.4%) constitute the most common allergens in the skin tests. Blok et al.'s study, on the other hand, demonstrated sensitivities to house dust (43%), grass (21%), wood (16%), cat hair (20%), and weeds (4%). In a study conducted in Yedikule Chest Diseases Hospital, skin tests were found to be positive in 23.8% of the cases, and they claimed that dermatofhagoides were the most common antigens among B. asthmatic patients in Turkey. Mites, grass, mold, and woodwere the most common antigens in a study of skin tests done in the USA. Supported by most studies, it is concluded that screening for house dust and mixed grass pollen can be sufficient, which complies with our work.

One-third of the patients were receiving prophylactic treatment, and the vast majorities were using ketotifen. In addition, the majority of our study population was between the ages of 3 and 5 years. There were difficulties in the supply of nebulizer and inhalermedications due to the disadvantaged socioeconomic status of the patients. Additionally, the soothing effects of ketotifen in allergic rhinitis, urticaria, and food allergy, as well as the ease of oral use have been the reasons for this preference. In children at an appropriate age, who may be more cooperative, cromolyn and steroids may be used more frequently with a spacer device.

The most common treatments in the emergency department were salbutamol (puff, nebulizer), adrenaline, intravenous perfusion (IVP) steroid at a dose of 2 mg/kg, and IVPaminophylline. The severity of asthma should be categorized at the emergency ward as mild, moderate, or severe and the peak flow value should be recorded. The treatment should be tailored accordingly[31]. In moderately severe asthmatics suffering from acute exacerbations, steroidsusually achieve control of the symptoms, improvement in lung functions, and a reduction in bronchial hyperresponsiveness. Oralprednisolone initiated in the emergency department reduces the hospitalization rate. Oral administration is as effective as the intravenous route. However, there is no increased benefit at doses above 2 mg/kg [32]. It has been noted that the use of aminophylline in addition to steroids and beta agonists (inhaler) does not provide additional benefit [33].

The frequency of antibiotic use increases parallel to the frequency of sinusitis. However, considering the other available data, it is observed that there is an excess in the use of antibiotics.

Of the patients, 67% came to their control visits. In the United States, 76% of the 348 patients followed closely in a university hospital came to their follow-ups and 19% of them were followed up more frequently[27]. Standardized history-taking, spirometer measurements, histamine provocation test, and skin tests are used during the follow-up and diagnosis [27,34]. In our study, 1/3rdof the patients did not come for follow up. Patients under regular follow-up are less likely to have sudden attacks, also giving the medical team an opportunity for patient and family education.

Conclusion

Consistent with the previous literature, male sex, and 3-5-year-old age group were observed as likely risk factors. Doctors should consider this finding when serving their patients. The similarity of annual admission rates during the studied years indicates that there is no change in asthma frequency in the population over time. For a chronic disease such as asthma, the high number of hospitalizations isimportant concerning the compliance with treatment as well as increased health expenses. However, effort should be given to reduce the number of hospitalization days. To avoid the use of high and unnecessary antibiotics, treatments must be implemented according to the rules of rational antibiotic use. Training and awareness programs for doctors, patients and pharmacists should be conducted in this regard. Patients should be avoided from known allergens, for which patient and family educations are invaluable.

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Original Article

Effects of Saint John's wort on the fetus in pregnant rats

Gebe sıçanlarda kantaron otunun fetüse etkisi

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ABSTRACT

Introduction: Because of the toxic and teratologic side effects that might develop into the fetus, the number of drugs that can be used in the treatment of depression seen in pregnancy is very limited. In this study, we investigated whether the Saint John's wort used during pregnancy has side effects on the liver of fetus.

Methods: Thirteen Wistar albino female rats were used in this study. The animals divided into two groups as 8 rats for the experimental group and 5 rats for the control group. The animals detected for pregnancy in the experimental group were fed with the Saint John's wort extract as 100 mg/kg/day through orogastric probe from the first day of the pregnancy. The animals in the control group were fed with 2 ml distiled water through an orogastric probe every day begining from the first day of the pregnancy. The newborn pups were taken. Their liver tissues were harvested and investigated after the tissue processing and staining procedure.

Results: Microvesicular lipidosis and hydropic degeneration were observed in histopathological evaluation of the harvested tissues of experimental group.

Conclusion: As a result, there is not enough data in the literature in order to claim that Saint John's worth is reliable for the pregnant women or fetus. It is important for the physician to evaluate the complaints related to the use of pregnancy and to raise the awareness of the physicians in the first stage of the pregnancy follow-up. For the usage of this herb as an alternative or addition to antidepressive drugs more preclinical (basic) and clinical studies need to be performed.

Keywords: Saint John's wort, fetus, liver

ÖZ

Giriş: Fetüste gelişebilecek toksik ve teratolojik yan etkilerinden dolayı, gebelikte görülen depresyonun tedavisinde kullanılabilecek ilaç sayısı oldukça sınırlıdır. Çalışmamızda, gebelik sırasında depresyon tedavisi için halk arasında sık kullanılan kantaron otunun fetüs karaciğeri üzerine yan etkilerini araştırdık.

Yöntem: Çalışmada kullanılan 13 adet dişi Wistar albino sıçan, 8 adet deney grubu, 5 adet de kontrol grubu olmak üzere ayrıldı. Gebe kalmaları sağlanan deney grubundaki hayvanlara, gebeliğin ilk gününden itibaren, gebelik süresince 100 mg/kg/gün kantaron otu ekstresi orogastrik sonda yardımıyla verildi. Kontrol grubundaki sıçanlara ise gebeliğin ilk gününden itibaren her gün 2 ml distile su orogastrik sonda yardımıyla verildi. Doğan yavruların karaciğer dokuları çıkarıldı, %10 nötral formalin ile fiksasyonu yapıldı, alkol takibinden sonra parafin blokları hazırlandı, alınan kesitler hematoksilen ve eosin ile boyanarak incelendi.

Bulgular: Deney grubuna ait karaciğer dokularının histopatolojik değerlendirmesinde mikroveziküler yağlanma ve hidropik dejenerasyon gözlendi.

Sonuç: Kantaron otunun gebe kadınlar veya fetus açısından güvenilir olduğunu iddia etmek için yeterli bilgi bulunmadığı sonucuna varıldı. Bu otun gebelik kullanımıyla ilgili sakıncaların hekimler tarafından değerlendirilmesi ve özellikle birinci basamakta hekimlerin, gebe takiplerinde hastaları bu konuda bilinçlendirmesi önem arz etmektedir. Kantaron otunun gebelikte kullanımı ve gerek anne gerek fetüste tüm vücuttaki etkilerinin ortaya konması için daha ileri çalışmalar yapılması gerekmektedir.

Anahtar Kelimeler: Kantaron otu, fetüs, karaciğer

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Introduction

Saint John's Wort (Hypericum perforatum) is a plant of the Hypericaceae family [1]. In various regions of Turkey, it is known as "Binbirdelik otu", "Kılıç otu", "Mayasıl otu", "Yara otu", and "Kuzu kıran" [2]. Saint John's Wort has been used since ancient times in psychiatric diseases, wound healing, digestive problems, burns, and infections [1]. Especially because of its antidepressant effect, it reaches millions of dollars sales every year in the United States and Europe [3]. It has been reported in Germany that this herb is prescribed more than antidepressant drugs [4].

At least nine groups of substances are shown contributing to the pharmacological effects of Saint John's Wort [5]. From these substances, it has been reported that hypericin and hyperforin are the predominant molecules responsible for the antidepressant effects of the plant [6,7]. These molecules may inhibit the enzyme monoamine oxidase (MAO), and may also lead to an increase in serotonin, dopamine, and norepinephrine levels [8].

Saint John's Wort has been used as a remedy in psychiatric disorders since ancient times. Hippocrates and Galen are also reported to use this herb to rescue people from the evil spirits [9]. Presently, its use as an herbal alternative to synthetic antidepressants has worldwide popularity. In the treatment of mild to moderate depression, this herb was proved to be as effective as synthetic antidepressant medications with perfect tolerability [10].

Depression reduces the quality of life by deteriorating human function, creativity, happiness, and satisfaction, and leads to substantial workforce losses [11]. International studies indicate that vast majority of depression is seen among women between the ages of 18 and 44, including fertility processes such as pregnancy, childbirth, and puerperium [12, 13]. These processes are a part of the natural life of women, which include a high risk of encountering many important biological and psychosocial changes and the risk of facing factors that can cause anxiety and stress [14]. Mild to moderate depression is the most common psychiatric disorder in pregnancy. Depression during pregnancy can create some biological risks for the mother and the baby [13].

Called "the herbal Prozac", the Saint John's Wort is frequently used in the population [15, 16]. Among women, who are more prone to use alternative treatment methods, this herb is usually accepted as harmless due to its natural origin. Therefore, the Saint John's Wort can be consumed uncontrolled in all periods of the pregnancy, exposing the fetus to side effects of this plant [17].

However, if we look at the literature, it is seen that the effects of this herb on the fetus have not yet been clarified. The effects of the plant on fetal growth and development, as well as the possible pathological effects on the liver, where the agent is metabolized, are vastly obscure.

This study aimed to evaluate the histopathological effects of non-prescribed and uncontrolled Saint John's Wort use on the fetal liver tissue in the treatment of depressive symptoms during pregnancy, and also to investigate its effects on the height and weight of the newborn, revealing the effects on growth and development.

Methods

Sheltering of the Animals

Thirteen female Wistar Albino rats obtained from Gaziantep University Medical Faculty Experimental Animals Laboratory and weighing between 170-200 grams were used in the study. Before starting the experiment, the animals were separated from each other for one week, put into wire chambers in rooms where ambient light was set at 12 hours light and 12 hours dark, and the room temperature was fixed at 21 ± 1 °C for acclimatization. During the experiment, all animals were fed with standard feed and tap water.

For the experiment, consent was obtained from the Gaziantep University Animal Experiments Local Ethics Committee with the approval number 06-2008 / 113.

Experimental Model

The rats were randomly assigned into experimental (8 rats) and control (5 rats) groups. The two groups were as follows:

Group 1: Control group (Given distilled water; n=5)

Group 2: Experimental group (Given Saint John's Wort; n=8)

The animals in the experimental group were placed in two cages, with four animals in each. All of the animals in the control group remained in the same cage. One male animal was placed into each cage. All female animals were followed up every other day by a vaginal smear method. Pregnant animals were taken into single cages. From the first day of the pregnancy on, all animals in the experimental group were given 100 mg/kg/day standardized Saint John's Wort extract in 2 ml of distilled water by gavage. Animals in the control group were given 2 ml of distilled water every day from the first day of pregnancy by an orogastric probe. The pregnant animals were allowed to deliver by the normal vaginal route. Immediately after birth, five randomly born pups from each mother in both groups were taken from the cages and included in the experiment (Figure 1). The other offsprings were excluded from the study.

After measuring and recording height and weights, the pups were sacrificed under anesthesia, followed by a laparotomy where the right lobes of the livers were removed and put into 10% neutral buffered formalin.

Histopathological Evaluation

After routine histological follow-up, three sections of 5-6 micron thickness (each section followed by 15 skipped sections) were taken from the liver tissues embedded in paraffin. The sections were stained with hematoxylin-eosin. The stained preparations were evaluated histopathologically and photographed on an Olympus BX50 light microscope. The evaluation was based on two criteria: Microvesicular steatosis and hydropic degeneration. Scoring of the findings was done as follows:

0: No lesion at all

1: Mild damage

2: Medium damage

3: Severe damage

Each criterion was evaluated using all three sections from each animal, and the mean values were reported.

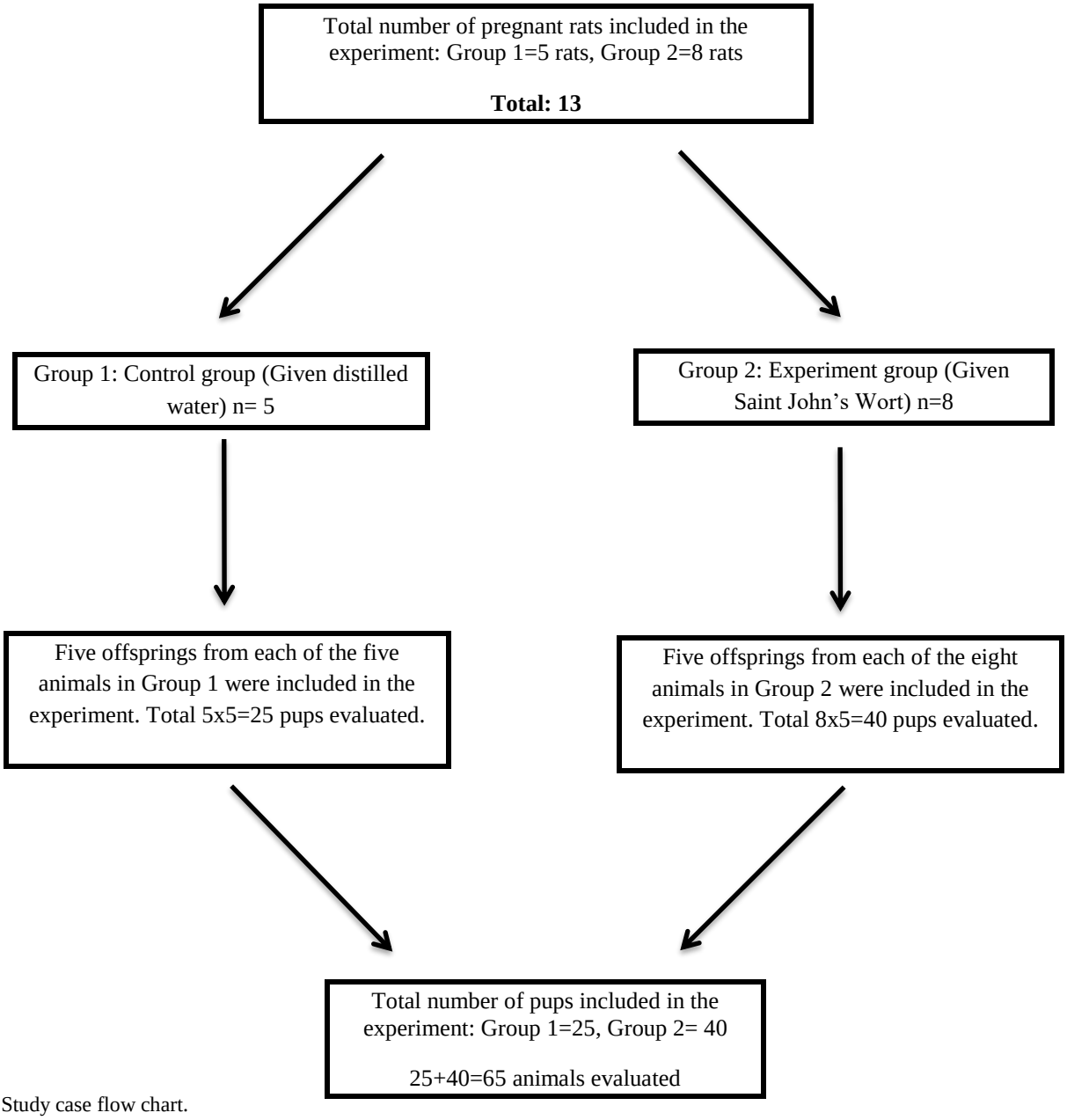

Figure 1. Study case flow chart.

Statistical analysis

Statistical analyzes of the results were done using the SPSS (SPSS Inc., Chicago, IL, USA) 13.0 package program. The results were analyzed using Student t and Mann Whitney U tests. A p value of <0.05 was considered significant.

Results

Clinical Observation

There were no differences in the clinical appearance of the animals in the study and control groups. Also, there was no difference between the offsprings of both groups. The number of puppies born from the rats in the control group ranged from 9 to 15 (mean 11.2), and the number of puppies from the rats in the experimental group ranged from 8 to 15 (mean 8.8). There was no statistically significant difference between the numbers of pups of the two groups ($p = 0.316$).

Histopathological Findings

In the histological sections, a normal liver structure with hematopoiesis in some areas was observed in the liver tissues of the control puppies (Figure 2).

Areas of hematopoiesis were also observed in the tissue sections of the pups in the experimental group. Apart from this, general organ structure was preserved, but microvesicular type of areas with steatosis were widely observed. Besides, frequent hydropic degenerations were observed in the hepatocytes (Figure 3-6).

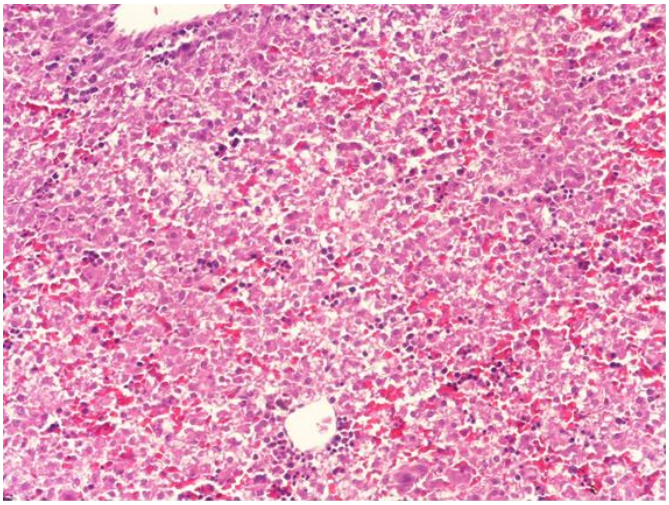

Figure 2. A hepatic section from the control group (10x20 magnification). Normal liver structure and hepatocytes at central vein and surroundings are seen. Also, hematopoiesis could be differentiated in some areas.

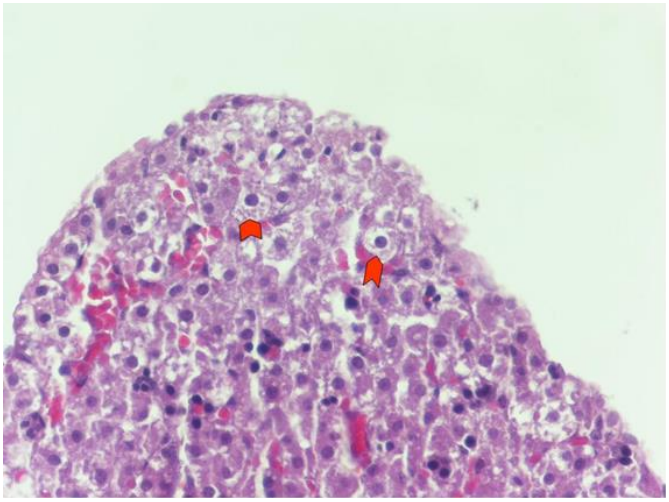

Figure 3. Hepatic section (10x40 magnification) taken from the group given Saint John's Wort. Arrowheads indicate areas of hydropic degeneration.

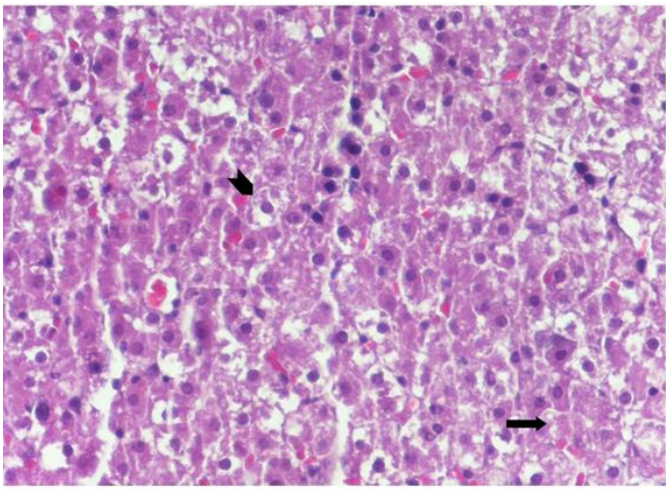

Figure 4. Hepatic section (10x40 magnification) taken from the group given Saint John's Wort. Arrow indicates microvesicular steatosis; arrowhead shows hydropic degeneration.

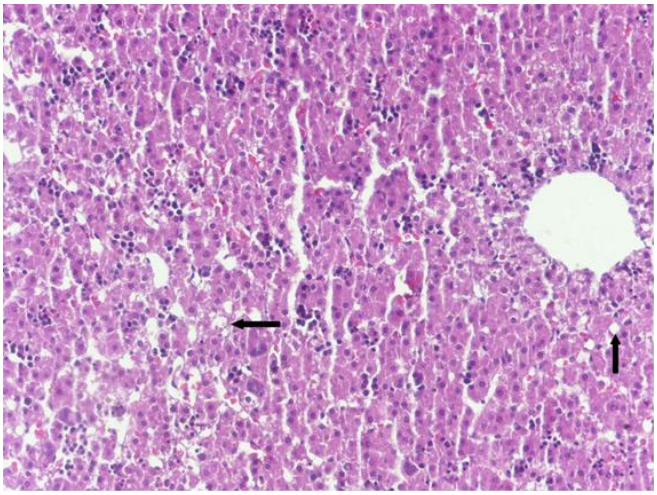

Figure 5. Light microscopic appearance (10x20 magnification) from the group given Saint John's Wort. Arrows indicate areas of microvesicular steatosis. Areas of continuing hematopoiesis are observed.

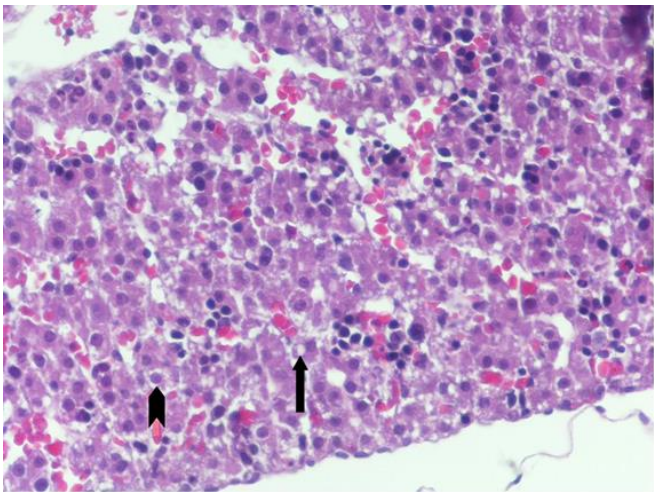

Figure 6. Hepatic section (10x40 magnification) taken from the group given Saint John's Wort. The arrow shows areas of microvesicular steatosis, arrowhead showing hydropic degeneration areas. Occasional hematopoiesis areas are seen.

Histopathological findings of the experimental group were significantly different when compared with the control group ($p < 0.05$) (Table 1).

Table 1. Comparison of histopathological findings of the control and experimental groups (Mann-Whitney U test)

Histopathological findings	Control group (n=25)	Experimental group (n=40)	p-value
Microvesicular steatosis ± SEM	0.067±0.0376	0.782±0.0916	<0.050
Hydropic degeneration ± SEM	0.022±0.0222	1.048±0.1112	<0.050

Evaluation of Growth and Development

When the birth weights and heights of the pups were measured, significantly lower birth weights were found in the experimental group compared to the control group ($p < 0.05$). However, there were no significant differences between the groups concerning heights ($p > 0.05$) (Table 2).

Table 2. Comparison of mean heights and weights of the control and experimental group pups (Student t-test)

Mean values	Control group (n=25)	Experimental group (n=40)	p-value
Mean height (mm±SEM)	40.24±0.230	40.20±0.277	>0.05
Mean weight (gr±SEM)	5.6713±0.05646	5.3436±0.07144	<0.05

Discussion

There are two case reports in the literature about the use of Saint John's Wort in pregnancy. In the first case, except for maternal thrombocytopenia and neonatal jaundice, no significant side effects attributable to Saint John's Wort were observed. In the other case, it was reported that the baby was healthy at birth, with normal birth weight and APGAR scores. Also, the physical examination, laboratory results, as well as the behavioral tests performed on days 4 and 23 were normal [18]. None of the cases discussed in the available literature report low birth weight or growth and developmental issues. In this work, however, offsprings of the rats given the St. John's Wort during pregnancy had significantly lower birth weights compared to the control group. This contradicts the normal birth weights seen in the literature. However, since the results in the available case report belong to a single case, they do not bear strong clinical significance; it could possibly be comparable to our results if observed in a patient group. In our study, the values of 65 pups were examined, and the results were compared statistically. It is known that the data obtained in this way are more reliable than the results of individual cases. Besides, the baby's birth weight in the case report may not be affected because the St. John's Wort was used after the 2nd trimester of the pregnancy. However, in our study, the pregnant rats were exposed to the St. John's Wort right from the diagnosis of the pregnancy throughout the gestation, including the first trimester, the period of essential organogenesis. The low birth weight may be explained by this long exposure period.

In a controlled cohort study of the use of the Saint John's Wort in pregnancy, 54 women who had used this herb during certain periods of their gestation were studied and found that infants born after intrauterine exposure did not have adverse outcomes compared to those who did not receive the herb [19]. Unlike in our study, pregnant women in this study used Saint John's Wort only for a certain period of the pregnancies. In the majority of the patients included in the literature, there is a rather short duration of exposure. However, in our study, the Saint John's Wort was given during the entire pregnancy period from the first day on. This includes both the first trimester of organogenesis and the second and third trimesters of the growth and development. Due to this significant difference, the reported literature may lack findings regarding low birth weight.

A variety of animal studies on the use of the Saint John's Wort during pregnancy are available in the literature. Chan et al. [20] have shown that hypericin, one of the active ingredients of the Saint John's Wort, is teratogenic on rat embryos at clinical doses used for humans. The results of this study are similar to our findings. However, in our current study, the effects of the Saint John's Wort on the liver were determined as hydropic degeneration and microvesicular steatosis, which cannot be considered as teratogenic. The teratogenic effects found by the above-mentioned article were not observed in our study, and it was observed that the development of the offsprings was normal in the physical and intrauterine examination. The conclusions reached by Chan et al. were drawn from studies performed in the cell culture medium. However, in vitro and in vivo effects of a substance can be different. An effect seen in the culture medium may not be observed in an in vivo environment. In some cases, even the opposite may be true. Our results are more appropriate in reflecting the in vivo effects of using the Saint John's Wort. In this regard, we believe that clinical outcomes may be more accurate in reflecting the likely effects.

In a study of Sprague-Dawley rats, Cada et al. [21] found that the Saint John's Wort did not cause behavioral changes in the fetuses. In our study, no behavioral parameters were observed, and the offsprings were sacrificed following postpartum height and weight measurements. In their studies on mouse pups, Rayburn et al. could not show a significant difference in cognitive, behavioral, growth, and physical maturation, but found that the birth weights of male pups were significantly lower than those in the placebo group [22-24], which is similar to our results. However, in our study, the offsprings were not separated by sex, and the results were evaluated together. This difference can be considered as a limitation of our work.

No detailed histopathological analysis has been performed in any of these studies, and the toxicity of the Saint John's Wort taken during pregnancy has not been evaluated at the tissue level. However, the most accurate method for claiming the reliability of using a substance is by revealing its

histopathological effects. The presence of tissue damage indicates that the substance is harmful, and thus, its use is not safe. For this reason, in this study, we gave the rats a standardized concentration of 100 mg/kg/day Saint John's Wort extract from the first day of pregnancy until birth. Immediately after birth, we measured the height and weights of the offsprings to determine whether the herb had any effects on growth and development and whether they had any toxic effects on the fetal liver by subjecting the offspring's liver tissues to histopathological examination.
In our study, when compared with the control group, the pups of the Saint John's Wort-fed rats had statistically significant damage to the liver tissues ($p < 0.05$). This damage was in the form of hydropic degeneration and microvesicular steatosis. In a study conducted at the dose of 100 mg/kg/day, consistent with our study, liver damage was found in the offsprings in the form of serious hepatocyte damage with vacuolization. However, in this study, the application of the Saint John's Wort to the animals was started two weeks before pregnancy and continued during pregnancy and the postpartum 21-days period [25]. In this study, the animals received the Saint John's Wort for a longer duration. In our study, although the concentration of the Saint John's Wort was taken only during pregnancy, the same level of liver damage and liver toxicity findings were observed. Besides, our study tried to model the use of this plant against depressive symptoms during pregnancy. The current literature, on the other hand, includes the use of the plant before pregnancy, as well as during pregnancy and lactation [25].

We observed that the birth heights of the offspring of the mothers who were exposed to the Saint John's Wort during pregnancy did not show a statistically significant difference when compared to the control group, but the birth weights were significantly lower than the control group. In a similar study, the birth weights of the offspring were not different from the control group [25]. In our study, 100 mg/kg/day of the Saint John's Wort was applied during pregnancy, and the offspring had lower birth weights compared to the control group. However, in the literature, even though the animals received the same dose during pregnancy starting from two weeks before gestation, the birth weights were not affected. In this study, three animals were used in each of the experiment and control groups. Having no statistically significant difference between the birth weights of the experimental and control groups may be due to the insufficient number of subjects; we had a substantially higher number of pups (65 pups born from 13 mothers).

In the literature, where pregnant rats received Saint John's Wort at a dose of 36 mg/kg/day during the 9-15th days of the organogenesis period, fetal birth weights of the control and experimental groups were compared, and no statistical difference could be demonstrated [26]. The reason for the Saint John's Wort not influencing the birth weights of the offspring might be related to the quite low dose compared to the 100 mg/kg/day dose used in our study and Saint John's Wort being applied for only 7 days during pregnancy; in our study, the Saint John's Wort herb extract was used throughout the pregnancy until birth. The reason for this was to investigate the effects of using this herb against the symptoms of depression during pregnancy, especially in the last trimester.

In this study, we tried to demonstrate histopathologically the toxic effects of using Saint John's Wort in pregnancy on the fetal liver tissue. However, we did not investigate the effects of this herb on other tissues of the fetus. In particular, we consider having not included studying the toxicity in the kidney and lung tissues as a limitation of this study. Besides, the fetal liver damage was histopathologically proven but not supported biochemically. The lack of studying biochemical liver function tests is another limitation of our study.

Conclusion

In conclusion, the present study showed that feeding rats with Saint John's Wort during pregnancy caused low birth weight in the fetus. It was also demonstrated histopathologically that the Saint John's Wort caused toxic damage to the liver tissue. Histopathological changes were observed as microvesicular steatosis and hydropic degeneration. It is essential for the physicians (especially the primary care physicians) to be aware of the risks and evaluate the use of this herb during pregnancy and to raise the awareness of the pregnant women during routine follow-ups. Further studies are needed to determine the safety of using the Saint John's Wort during gestation and study its effects on all organ systems of both the mother and the fetus.

Conflict of interest: None
Financial support: None

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Original Article

A relationship between subclinical hypothyroidism and hematologic parameters in patients with Down Syndrome

Down Sendromlu hastalarda subklinik hipotiroidizm ve hematolojik parametreler arasındaki ilişki

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ABSTRACT

Introduction: Down syndrome (DS) which is defined as trisomy 21 is the most common chromosomal defect characterized by mental retardation, hypotonia, dysmorphic facial features, and other distinctive phenotypic characteristics. The prevalence of thyroid disorders in DS is 3% and is significantly higher than in the normal population. In this study we aimed to investigate hematologic parameters of children with DS who had and hadn't subclinical hypothyroidism and compare them with healthy controls.

Methods: This study included 184 patients who were followed up with genetically diagnosed DS. Complete blood count, levels of serum electrolytes, glucose, urea, liver function tests, thyroid function tests were reviewed.

Results: 102 (55.4%) of the patients with DS were male and 82 (44.6%) were female. Mean age was 6.2 ± 4.0 years. Control group was constituted of outpatient healthy children. White blood cell count, hemoglobin, hematocrit, and neutrophil counts were found to be significantly lower in patients with DS. Platelet count and plateletcrit levels were found to be higher and platelet distribution width was lower in patients with DS than in the control group.

Conclusion: We found significant differences among hematological parameters in patients with DS. Subclinical hypothyroidism influences red blood cell distribution width, platelet count and MPV. Knowing the incidence and severity of hematologic abnormalities in patients with DS will be beneficial during follow-up in clinical practice.

Keywords: child, down syndrome, hematological parameters, hypothyroidism

ÖZ

Giriş: Trizomi 21 olarak tanımlanan Down sendromu (DS) mental retardasyon, hipotoni, dismorfik yüz özellikleri ve diğer ayırt edici fenotipik özellikleri ile karakterize en sık görülen kromozomal defekttir. DS'de görülen tiroid bozukluğu prevalansı % 3'dür ve normal popülasyona göre anlamlı derecede yüksektir. Bu çalışmada, subklinik hipotiroidisi olan ve olmayan DS'lu çocukların hematolojik parametrelerini araştırmayı ve bunları sağlıklı kontrollerle karşılaştırmayı amaçladık.

Yöntem: Çalışmaya genetik olarak tanısı konan ve takip edilen DS'li 184 hasta dahil edildi. Hastaların tam kan sayımı, serum elektrolit seviyeleri, glikoz, üre, karaciğer fonksiyon testleri ve tiroid fonksiyon testleri gözden geçirildi.

Bulgular: DS'lu hastaların 102'si (% 55,4) erkek, 82'si (% 44,6) kadındı. Yaş ortalaması 6,2 ± 4 yıl idi. Kontrol grubu, polikliniğimize başvuran sağlıklı çocuklardan oluşturuldu. DS'lu hastalarda kan sayımı, hemoglobin, hematokrit ve nötrofil sayıları anlamlı olarak düşük bulundu. Yine DS'li hastalarda kontrol grubuna göre trombosit sayısı ve trombosit düzeyleri daha yüksek bulunurken trombosit dağılım genişliği daha düşük bulundu.

Sonuç: DS'li hastalarda hematolojik parametreler arasında anlamlı farklar bulduk. Subklinik hipotiroidizm, eritrosit dağılım genişliğini, trombosit sayısını ve MPV'yi etkiler. DS'li hastalarda hematolojik anormalliklerin sıklığını ve şiddetini bilmek, klinik uygulamada takip sırasında yararlı olacaktır.

Anahtar Kelimeler: Çocuk, Down sendromu, hematolojik parametreler, hipotiroidizm

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Introduction

Down syndrome (DS) which is defined as trisomy 21 is the most common chromosomal defect characterized by mental retardation, hypotonia, dysmorphic facial features, and other distinctive phenotypic characteristics. The incidence of DS is approximately 1 in every 733 live births. While 95% of the cases have 3 copies of chromosome 21, 4% have translocation at chromosome 21 and 1% are mosaics. Advanced age (>35) of mother is attributed as the major cause of trisomy 21 [1].

Hematological disorders are frequently seen in DS. It is known that various abnormalities are observed in all three hematopoietic cell lines. Leukemia-like transient proliferative disorder, increased leukemia incidence, neutrophilia, thrombocytopenia, polycythemia, thrombocytosis and anemia are common haematological abnormalities seen in the course of DS [2].

The prevalence of thyroid disorders in DS is 3% and is significantly higher than the normal population. The most common thyroid disease in this syndrome is subclinical hypothyroidism (SCH). The biochemical condition of elevated TSH and normal triiodothyronine (T3) and thyroxine (T4) levels is defined as SCH. Hypothyroidism or thyroid dysfunction can be congenital or acquired in patients with DS. Therefore, patients with DS should be followed up periodically for thyroid functions since birth [3-5].

While thyroid hormones regulate the metabolism and proliferation of blood cells, they have an important role in hematopoiesis. Hypothyroidism is one of the most common diseases of the endocrine system that affects all systems including the hematopoietic system. It has been shown that three main components of hematopoiesis; erythropoiesis, lymphopoiesis and myelopoiesis, are affected by hypothyroidism [6].

To the best of our knowledge there is no study investigating the association of thyroid disorders and hematologic parameters in patients with DS. In this study we aimed to investigate hematologic parameters of children with DS who had and hadn't subclinical hypothyroidism (SCH) and compare them with healthy controls.

Methods

This study included 184 patients who were followed up with genetically diagnosed DS and SCH in pediatrics departments of Necmettin Erbakan University Meram Medical Faculty and Selcuk University Medical Faculty between January 2011 and July 2017. Ethical approval of the study was taken from the ethics committee of Meram Medical Faculty of Necmettin Erbakan University. Patients' data were reviewed retrospectively and demographic characteristics recorded. Complete blood count, levels of serum electrolytes, glucose, urea, liver function tests, thyroid function tests were reviewed. The white blood cell count (WBC), absolute neutrophil count (ANC), absolute lymphocyte count (ALC), neutrophil to lymphocyte ratio (NLR), red blood cell distribution width (RDW), platelet count and MPV, Platelet distribution width (PDW) and Plateletcrit (PCT) values were obtained from the hemogram results. Patients who had high TSH (TSH> 4 IU / L) and normal free T4 levels were diagnosed as SCH.

The study population was classified into three groups; Group 1: DS patients without SCH; Group 2: DS patients with SCH; Group 3: control group. Patients with gastrointestinal system, cardiovascular system involvement or who had other diseases (i.e. diabetes mellitus, epilepsy, asthma, hypertension and immunodeficiency) and patients using any drug were not included in the study. Control group was constituted of outpatient healthy children with normal physical examination, who did not have any chronic illness or sign of any infection and undergone blood analyses for other reasons (i.e. routine coheck-up, poor apetite, abdominal pain).

Statistical analysis

Statistical methods of descriptive data were shown as mean±standard deviation. The Kolmogorov-Smirnov and Shapiro-Wilk tests were applied to check the distribution of parameters. While parametric data were analyzed using student's t-test, nonparametric were analyzed with chi-square and Mann-Whitney U test. Kruskal-Wallis test was used to compare groups. Spearman correlation test was applied for the correlation analysis of the parameters. Results were considered as significant if $p < 0.05$. SPSS 21.0 (SPSS Inc., Chicago, IL, USA) packet computer program was used for statistical analysis of datas.

Results

102 (55.4%) of the patients were male and 82 (44.6%) were female and the mean age was 6.2 ± 4.0 years. The control group was consisted of 36 males (43.9%) and 46 females (56.1%) with a mean age of 6.9 ± 3.5 years. Demographic and laboratory characteristics of patients are given in Table 1. When patients with DS were compared with control group; WBC, ANC, hemoglobin and hematocrit were found to be significantly lower in patients with Down syndrome (p values: 0.039, 0.004, 0.042, 0.014, respectively). However, no statistically significant difference was found between the two groups in terms of NLR, RDW and ALC. The comparison of platelet indices revealed that platelet count and PCT levels were found to be higher and PDW ratio was lower in patients with DS than in the control group, and these differences were statistically significant. However, there was no statistically significant difference in terms of MPV values.

Table 1. Demographic and laboratory characteristics of patients and the control group

	Patients with DS (n=184)	Control group (n=82)	P value
Female/male	82/102	36/46	>0.05
Mean age (year)	6.28±4.02	6.98±3.56	>0.05
WBC (/mm^3)	7113±1973	7601±1669	**0.039**
ANC (/mm^3)	3277±1739	3628±1287	**0.004**
ALC (/mm^3)	3048±1205	3130±1060	>0.05
NLR	1.39±1,37	1.32±0.73	>0.05
Hb (gr/dl)	12.51±1.97	13.06±0.90	**0.042**
Hct (%)	37.11±5.31	38.70±2.41	**0.014**
RDW (%)	15.09±3.04	14.70±1.06	>0.05
Platelet indices			
PLT (x10^3 /uL)	355±133	305±640	**0.001**
MPV (fL)	8.20±1.88	8.24±0.76	>0.05
PCT (%)	0.83±1.22	0.23±0.09	**0.001**
PDW (%)	15.97±9.29	16.41±2.30	**0.001**

Data as means± SD, DS: Down Syndrom, WBC: White blood cell count, ALC: Absolute lymphocyte count, ANC: Absolute neutrophil count, Hb: Hemoglobin, MPV: Mean platelet volume, NLR: Neutrophil-to-lymphocyte ratio, RDW: Red cell distribution width, PLT: Thrombocyte count PCT: Plateletcrit PDW: Platelet distribution width, p value: p value of comparison between controls and DS

Table 2. Comparison of demographic and laboratory characteristics of patients according to study groups

	DS patients with SCH (n=57)	DS patients without SCH (n=127)	Control group (n=82)	P^1 value	P^2 value	P^3 value
Female/male	29/28	53/74	36/46	>0.05	>0.05	>0.05
Mean age (year)	7.04±3.52	5.93±4.20	6.98±3.56	>0.05	>0.05	>0.05
WBC (/mm^3)	7021±1702	7154±2088	7601±1669	>0.05	>0.05	>0.05
ANC (/mm^3)	3175±1526	3323±1831	3628±1287	>0.05	**0.016**	**0.01**
ALC (/mm^3)	3061±1116	3042±1247	3130±1060	>0.05	>0.05	>0.05
NLR	1.34±1.45	1.41±1.37	1.32±0.73	>0.05	>0.05	>0.05
Hb (gr/dl)	12.93±1.61	12.33±2.09	13.06±0.90	>0.05	>0.05	**0.008**
Hct (%)	38.33±4.31	36.56±5.64	38.70±2.41	>0.05	>0.05	**0.001**
RDW (%)	14.37±2.32	15.42±3.27	14.70±1.06	**0.034**	>0.05	>0.05
Platelet indices						
PLT(x10^3/uL)	387±159	340±117	305±64	**0.034**	**0.001**	**0.017**
MPV (fL)	7.67±2.09	8.44±1.74	8.24±0.76	**0.009**	>0.05	>0.05
PCT (%)	0.82±1.42	0.84±1.12	0.23±0.09	>0.05	**0.003**	**0.001**
PDW (%)	16.77±9.98	15.61±8.98	16.41±2.30	>0.05	>0.05	>0.05

Data as means± SD, DS: Down Syndrom, SCH: Subclinical hypothyroidism, WBC: White blood cell count, ALC: Absolute lymphocyte count, ANC: Absolute neutrophil count, Hb: Hemoglobin, MPV: Mean platelet volume, NLR: Neutrophil-to-lymphocyte ratio, RDW: Red cell distribution width, PLT: Thrombocyte count, PCT: Plateletcrit, PDW: Platelet distribution width, P^1: p value comparison between DS patients with SCH and DS patients without SCH, P^2: p value comparison between DS patients with SCH and controls, P^3: p value comparison between DS patients without SCH and controls.

There was no statistically significant difference between three groups in terms of gender. Comparison of demographic and laboratory characteristics of the three groups are given in Table 2. WBC, ALC and NLR levels showed no statistically significant difference when 3 groups were compared. ANC was statistically lower in both groups of DS than in the control group, however, no statistically significant difference was found between DS patients with SCH and without. When three groups were compared for PDW, hemoglobin and hematocrit levels, these were significantly lower in DS patients without SCH than both other groups. While RDW levels were significantly lower in DS patients with SCH than other groups, platelet count was significantly higher DS with SCH. There was a statistically significant difference between all the three groups when MPV levels were compared. PCT levels were significantly lower in the control group than others.

Discussion

In this study, we showed that hematological parameters were significantly affected in patients with DS when compared with control group. While WBC, PDW, hemoglobin, hematocrit, and neutrophil counts were found to be significantly lower in patients with DS, PLT and PCT levels were higher when compared with the control group. We found that ANC and PLT levels were affected more excessively in DS patients with SCH.

Thyroid hormones regulate the metabolism of all the cells in the human body, thus they play a major role in the metabolism of blood cells. Thyroid gland has important effects on erythropoiesis by the induction of erythropoetin secretion and the proliferation of erythroid progenitors at the same time [7]. Additionally hypothyroidism causes hypoplasia of all myeloid cell roots including anemia with different severity, thrombocytopenia, leukopenia, and even rare cases of pancytopenia [8]. Hypothyroidism also has negative effects on other blood indices including mean corpuscular volume (MCV), mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, hemoglobine, RDW, MPV. All these dysfunctions usually return to normal after treatment of the thyroid disorder [9]. The difference of hematological parameters between DS patients on thyroid hormone therapy and the groups suggests that this difference may be due to other mechanisms besides hypothyroidism.

The incidence of various hematologic abnormalities associated with DS has not been clearly defined. In the study of Miller et al. [10] which evaluated 81 infants with DS, hematological evaluation was done in 61 infants, and 33 had a normal hematological status, and 28 (46%) had at least one abnormality, including hematocrit, white cell count, or platelet count. Hord et al. reported that 66% of 25 newborns with DS had thrombocytopenia in their study [11].

The largest study evaluating hematologic abnormalities in newborns with DS in the United States involved 158 cases and neutrophilia (80%), thrombocytopenia (66%) and polycythemia (34%) were reported to be the most common hematological abnormalities. Thrombocytosis, anemia and neutropenia were rarely seen [3]. In the study performed by DW Kim et al, thrombocytopenia (35.1%) was the most common hematological abnormality in East Asian Newborns. Other common haematological abnormalities were neutropenia (16.2%), leukocytosis (10.8%) and polycythemia (10.8%). They showed that hematological findings recovered spontaneously in those patients [12]. In our study WBC levels was found to be lower in DS patients than in the control group. Leukocytosis was present in 22 and leukopenia in 5 patients. We think that SCH influences blood WBC levels. Also in our study, thrombocytosis was found in 20.6%, neutropenia in 10.32%, thrombocytopenia in 4.34% and neutrophilia in 2.17% of our patients. No patient had polycythemia. The first fact that our rates differ from other studies is that our patients were older and might have recovered spontaneously. The second, some of our patients had SCH, suggesting that SCH has an effect on hematological parameters. We think that the low ANC in our study are due to the suppressive effect of SCH on the bone marrow.

Weinberger and Oleinick reported that 15% of newborns with DS had polycythemia [13]. In subsequent studies, the prevalence of polycythemia in patients with DS was reported to be between 8% and 64% [10,11,14]. Widness and colleagues found that newborns with DS had elevated concentrations of erythropoietin in the umbilical cord blood and suggested that this caused polycythemia [15]. In our study, hemoglobin and hematocrit levels were found to be lower in patients with DS than in the control group. Hemoglobin and hematocrit levels were found to be lower in DS patients without SCH than in DS patients with SCH and the control group. Polycythemia was not detected in any of our patients.

RDW is part of a standard full blood count that measures the change in size and volume of the RBC. RDW is used in conjunction with MCV to determine the cause of anemia [16] There are no studies about RDW in patients with DS. Additionally, there are rare studies on the relationship between RDW and hypothyroidism. In a study of patients with thyroid dysfunction, Yu HM et al. showed that SCH and RDW were associated significantly when patients with SCH and the control group were compared [17]. RDW and serum TSH levels were reported to be associated significantly in another study [18]. In our study, we found that RDW was significantly higher in patients with DS compared to the control group. However, DS patients without SCH were found to have a higher incidence than DS patients with SCH. This suggests that DS has an impact on RDW.

In a large case series study, thrombocytopenia was identified as one of the most common hematologic abnormalities in about two thirds of infants with DS during the first week of life [12].The etiology of thrombocytopenia seen in DS is not fully understood. In a study evaluating thrombopoietin and platelet counts in newborn infants with DS, thrombocytopenia rate was 58% and the average TPO levels were reported to be not different from the control group of newborns without DS [18]. However, in the study of Kivivuori et al. that thrombocyte counts of neonates with DS were prospectively monitored, indicated that thrombocytopenia was usually short-term and then displaced by thrombocytosis [19]. In a study conducted by Kater et al. In 28 of 49 patients with congenital cardiac defects had DS. Thrombocyte counts of patients with DS reached to 100,000 / mm^3 on postoperative 6th day, whereas patients without DS reached on same day of cardiac surgery. It was hypothesed that the cause of thrombocytopenia seen in patients with DS may be due to a short-term decrease of thrombopoietin synthesis after cardiac surgery [20]. In our study, we found that the mean platelet count of DS patients was higher than the control group. DS patients with SCH had higher platelet count than DS patients without SCH and the control group. We have also found that SCH causes an increase in platelet levels in patients with DS. While thrombocytopenia (<150000 / mm3) was detected in 8 patients and 38 patients had thrombocytosis (> 450000 / mm3).

Platelet indices include MPV, PDW, and PCT. Platelets are closely related to hemostasis, inflammation, immune cell activation, tissue regeneration and other physiological and pathological processes [21]. Young thrombocytes released from the bone marrow due to inflammation reach larger sizes. Inflammatory mediators such as chemokines, cytokines, and procoagulant molecules are secreted by activated platelets. MPV, which reflects the platelet size and the speed of platelet production in the bone marrow, is a frequently used parameter to assess platelet activation and function [22]. MPV reflects platelet size and activity and is used as a measure of platelet dysfunction. Larger thrombocytes are thought to be more active and tend to be aggregated, thus leading to endothelial dysfunction. Larger and functionally more reactive platelets increase the tendency to thrombosis [23]. There are many studies in the literature on the role of MPV in different systemic diseases including cerebrovascular disorders and cardiovascular disorders. In addition, MPV has been reported to increase in patients with vascular risk factors such as diabetes, hypertension, hypercholesterolemia, smoking, and subclinical hypothyroidism [23,24]. Yımaz and colleagues found no association between hypothyroidism and MPV in their study [25]. In our study, we did not detect changes in MPV levels. Mean MPV levels in DS patients were not different from control group. However DS patients with SCH had lower MPV levels than DS patients without SCH and the control group.

PDW is another platelet activation marker. PDW increases in patients with thrombocytopenia due to an increase of young platelets by bone marrow response. PDW indicates platelet activation more specifically than MPV in the activation process [26]. There are studies in the literature that examine the relation of PDW with various diseases. PDW values were found to be significant in distinguishing patients with ITP and aplastic anemia. PDW was found to be increased in ITP. Platelet production increases due to platelet destruction in ITP and anisocytosis occurs. However, PDW was found to be low due to inadequate platelet production in the aplastic anemia [27]. In vasocclusive crisis of patients with sickle cell anemia, PDW was found to be increased. This is mainly due to increased coagulation and increased megakaryocyte volume [28]. In patients Kawasaki disease, PDW and MPV were found to be lower than healthy control group. This low level of MPV and PDW is attributed to the use of large active platelets in vascular events and to the erroneous production of thrombopoietin in inflammatory event [29]. In our study we found that mean PDW levels were lower in DS patients than in the control group. DS patients without SCH had lower PDW levels than DS patients with SCH and the control group.

PCT is the percentage of platelets in total blood volume. PCT is measured from platelet count and MPV. Below 0.1% of PCT is indicative of platelet transfusion indications and is indicative of a greater risk of bleeding than thrombocyte counts in thrombocytopenic patients. It may be useful in diseases where the platelet count is low but the diameter is large. Although platelet counts are low, platelet functions may be provided with large platelets, so it may be more useful to look at PCT level instead of platelet count [30]. Plateletcrit was found to be less than 1% in patients undergoing transfusion due to bleeding after cardiopulmonary bypass. This suggests that PCT is as important as the platelet count in thrombocytopenic patients [31]. It was determined that there was a significant relationship between platelet count and PCT suggesting that platelet count and platelet count are two important factors for hemostasis [32]. PCT levels were higher in DS patients than in the control group. In DS patients both with SCH and without hypothyroidism, it was found to be higher than the control group. We think that hypothyroidism affects thrombocyte indices in patients with DS.

Limitations

As our study was a retrospective study, it didn't cover our prospective observations. Since patients with hypothyroidism are obliged to receive replacement therapy, we were not able to exclude these patients from the study. Additionally, thyroid hormone therapy might have affected hematological parameters.

Conclusion

We found significant differences among hematological parameters including WBC, neutrophil count, hemoglobin, hematocrit, platelet count, PDW and PCT values in patients with DS. The results indicated that SCH influences RDW, platelet count and MPV. Knowing the incidence and severity of hematologic abnormalities in DS patients will be beneficial for physicians in clinical practice.

Conflict of interest: None

Financial disclosure: None

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Original Article

Assessment of the signs of anxiety and depression in relatives giving care to cancer patients hospitalized in the palliative care service

Palyatif bakım servisinde yatmakta olan kanser hastalarına bakım veren yakınlarının anksiyete ve depresyon belirtilerinin değerlendirilmesi

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ABSTRACT

Introduction: Previously, palliative care was an approach brought forward in terminal patients when treatment options were exhausted. However, today, the opinion that palliative care should be initiated in addition to other treatment modalities starting from the moment of diagnosing a life-threatening disease has become prominent. The symptoms of depression and anxiety are common in patients with chronic diseases such as cancer. Moving on from the fact that these findings also manifest in the relatives of patients, this study aims to identify the symptoms of depression and anxiety and to assess these symptoms in the relatives of patients hospitalized in the extensive palliative care center.

Methods: Designed as a descriptive cross-sectional study, this survey included a single group without control and was performed by conducting face-to-face interviews after obtaining consent from patient relatives. The questionnaire prepared consisted of the Beck anxiety scale (BAS), Beck depression scale (BDS), the hospital anxiety and depression scale (HADS) together with sociodemographic variables. The study included 102 volunteers and was carried out over a three-month period. Sociodemographic data of the patients were summarized using descriptive statistics. Subgroup analyses were performed using appropriate parametric and non-parametric tests.

Results: The study enrolled 102 participants providing care to a relative in the palliative care service. Among these, 61 (59.8%) were women, and 41 (40.2%) were men. The risk for depression was identified as 43.1% (n=44) according to the BAS, and as 91.2% (n=93) according to the HADS. The anxiety rate was 66.7% (n=68) according to the BAS. Among these, 36.7% (n=25) demonstrated mild anxiety, 30.8% (n=21) demonstrated moderate anxiety and 32.3% (n=22) demonstrated severe anxiety. According to HADS, the risk for anxiety was 72.5% (n=74).

Conclusion: The fact that the presence of depression and anxiety was significant in the caregivers of patients in the palliative care service warrants careful follow-up and necessary support of both the patients and their caregivers for mood disorders.

Keywords: Palliative care, cancer, caregivers, anxiety, depression.

ÖZ

Giriş: Palyatif bakım, önceleri, tedavi edici yaklaşımların tükendiği, son dönem hastalarda gündeme gelen bir yaklaşımken, günümüzde, yaşamı tehdit eden hastalıkların tanısından itibaren, tedavi edici yaklaşımlarla ek olarak gündeme gelmesi gerektiği görüşü hakimdir. Kanser gibi kronik hastalıklarda depresyon ve anksiyete belirtileri sık olarak saptanmakla birlikte hasta yakınlarında da bu bulguların saptanmasından yola çıkılarak tasarlanan bu araştırmada kapsamlı palyatif bakım merkezinde yatarak tedavi görmekte olan kanser hastalarının yakınlarında depresyon ve anksiyete belirtilerinin saptanması ve değerlendirilmesi amaçlanmaktadır.

Yöntem: Tanımlayıcı-kesitsel tipte tasarlanan araştırma kontrol grubu olmadan tek grup üzerinden yapılan bir anket çalışması olup, hasta yakınlarının onamı alındıktan sonra, yüz yüze görüşme tekniği ile uygulandı. Hazırlanan anket, sosyodemografik değişkenler ile beraber, Beck anksiyete ölçeği (BAÖ), Beck depresyon ölçeği (BDÖ), hastane anksiyete ve depresyon ölçeği (HADÖ) bölümlerinden oluşmaktadır. Çalışma, üç aylık bir sürede 102 gönüllü ile yapıldı. Hastaların sosyodemografik verileri tanımlayıcı istatistikler kullanılarak özetlendi. Uygun parametrik ve non-parametrik testler kullanılarak alt grup analizleri yapıldı.

Bulgular: Çalışmamıza palyatif bakım servisinde yakınına bakım veren 102 katılımcı dahil olmuştu. Bunların 61'i (%59,8) kadın ve 41'i (%40,2) erkekti. Depresyon sıklığını incelemek amacıyla yapılan anketler sonucunda kanser hastalarına bakım verenlerde BDÖ'ye göre %43.,1 (n=44), HADÖ'ye göre %91,2 (n=93) oranında depresyon riski saptanmıştır. Anksiyete sıklığına bakıldığında; BAÖ'ye göre %66,7 (n=68) oranında anksiyete mevcuttu. Bunların %36,7'sı (n=25) hafif , %30,8'i (n=21) orta, %32,3'i (n=22) şiddetli anksiyete gösteriyordu. HADÖ ile %72,5 (n:74) oranında anksiyete riski mevcuttu.

Sonuç: Palyatif bakım servisinde hastalara bakım verenlerde ihmal edilemeyecek düzeyde depresif ve kaygılı duygu durum izlenmiş olması, hastaların yanı sıra bakım verenlerin de duygu durum bozukluğu açısından iyi gözlenmesi ve gerekli desteğin sağlanması açısından önemlidir.

Anahtar Kelimeler: Paltatif bakım, kanser, bakım verenler, anksiyete, depresyon.

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Introduction

According to the World Health Organization (WHO) definition, palliative care is an approach that improves the quality of life of patients and their relatives who are facing problems associated with life-threatening diseases and focuses on the early detection and treatment of physical, psychosocial, social, and spiritual issues. Previously, palliative care was an approach brought forward in terminal patients when treatment options were exhausted. However, today, the opinion that palliative care should be implemented in addition to other treatment modalities starting from the moment of diagnosing a life-threatening disease has become prominent [1].

Survival rates of the diseases increased parallel to the medical advances. These improvements have brought new problems to deal with. The family units have shrunk, the number of individuals involved in business life in the family has increased, and the number of individuals who could take care of a family member struggling with chronic illnesses has decreased in the twenty-first century. Risk factors such as traumatic life events, physical disorders, family disputes and conflicts that trigger the emergence of mental disorders have been described in 2004 WHO report under the topic "prevention of mental disorders" [2]. It is emphasized in this report that the long-term (chronic) health problems increase the risk of depression. One of the physical health problems of long-term life threat, ranked as one of the risk factors for mental problems, is cancer [3]. Depending on their disease and treatment methods, cancer patients are experiencing many physical and psychological symptoms such as loss of appetite, fatigue, muscle aches, decreased energy, dry mouth, gastrointestinal complaints, shortness of breath, and depression [4]. Caregivers of cancer patients have difficulty in managing the patient's symptoms and performing routine daily activities. It has been pointed out that the challenges associated with symptom management of caregivers cause some significant problems such as stress, anxiety, depression, fatigue, insomnia, excessive sleeping, loss of appetite, decreased activity, self-blame, concentration problems, and difficulty in decision making [5].

Cancer that requires a long-lasting treatment can negatively affect the quality of life by causing socioeconomic and psychological problems. Depression, which is at the top of these psychological/mental problems, is often overlooked or misdiagnosed because it is often masked by another disease. On the other hand, anxiety often accompanies depression. Anxiety in depressive mood episodes is a condition that complicates depression and makes treatment difficult. The symptoms of depression and anxiety are common in patients with chronic diseases such as cancer. Moving on from the fact that these findings also manifest in the relatives of patients, this study aims to identify the symptoms of depression and anxiety and to assess these symptoms in the relatives of patients hospitalized in the extensive palliative care center.

Methods

This study was approved by the Local Ethics Committee of İzmir Kâtip Çelebi University Atatürk Training and Research Hospital (Date: 11.11.2013, No 219). The descriptive cross-sectional study consisted of a single group that included cancer patients who applied to the İzmir Kâtip Çelebi University Atatürk Training and Research Hospital Palliative Care and Support Services. There was no control group. This survey was performed by conducting face-to-face interviews after obtaining consent from patient relatives. The data collection tool consisted of the Beck anxiety scale (BAS), Beck depression scale (BDS), the hospital anxiety and depression scale (HADS) together with sociodemographic variables.

Hospital Anxiety Depression Scale (HADS): The hospital anxiety depression scale (HADS) was designed by Zigmond and Snaith to detect significant anxiety and depression in general medical patients. Validity and reliability studies for the Turkish version of this inventory were performed by Aydemir et al. The purpose of the scale is not to diagnose, but to identify the risk group by rapidly screening anxiety and depression. The scale can also be used to monitor changes in the patient's emotional state. HADS comprises 14 items, seven of which relate to anxiety symptoms and seven to depressive symptoms. In Turkey, the anxiety sub-scale cut-off score was found as 10/11, and the depression subscale cut-off score as 7/8. It was reported that an anxiety score that is greater than 10 and the patients having depression scores over 7 can be classified as "under risk" patients [6].

Beck Depression Scale (BDS): The BDS consists of 21 self-rated questions, each answer scored on a scale of 0–3 summing up to a total ranging from 0 to 63. Validity and reliability study of the Turkish version of this inventory was performed by Teğin (1980) and Hisli (1989) [7].

Beck Anxiety Scale (BAS): The BAS scale was developed by Beck et al. in 1988 in response to the need for a scale that was able to distinguish anxiety from depression. It is designed to measure the experienced severity of anxiety symptoms. The Beck Anxiety Inventory consists of 21 items and is scored from 0 to 3. The validity and reliability study of the Turkish version of this inventory was performed by Ulusoy et al. in 1998 [7].

Statistical Analyses

No sampling was done for the current study. However, it was aimed to reach all caregivers who were hospitalized for a minimum of three months. Caregivers were excluded from the study if they were not willing to participate in the survey, had missing answers to survey questions, diagnosed psychiatric distress, and used drugs that can trigger depression or anxiety. Statistical analysis was performed with the Statistical Package for the Social Sciences (SPSS, IBM, Armonk, NY, USA). Socio-demographic data of the patients were summarized using descriptive statistics. The Chi-square test was performed for subgroup analyses. The significance level was set at $p<0.05$.

Results

Our study included 102 participants giving care to a relative in the palliative care service. Among these, 61 (59.8%) were women and 41 (40.2%) men. The majority (75.5%) of the participants were married (n=77) while 20.6% (n=21) and 3.9% (n=4) of all caregivers were single and widowed/divorced respectively. Of the participants, 40.2% (n=41) were graduated from high school or university. The demographic data of caregivers are given in Table 1.

Table 1. Demographic data and characteristics of caregivers

		n	%
Gender	Women	61	59.8
	Men	41	40.2
Marital status	Single	21	20.6
	Married	77	75.5
	Widowed / Divorced	4	3.9
Education status	Illiterate	6	5.9
	Literate	2	2.0
	Primary school	37	36.3
	Secondary school	16	15.7
	High school	21	20.6
	University	20	19.6
Monthly income	<500 TL	18	17.6
	500-1000 TL	49	48.0
	1001-2000 TL	17	16.7
	2001-3000 TL	9	8.8
	>3000 TL	9	8.8
Degree of proximity	First-degree relative	56	54.9
	Second-degree relative	8	7.8
	Third-degree relative	2	2.0
	Other	36	35.3

Of the caregivers, 54.9% were first-degree relatives and 7.8% second-degree relatives. Most of the caregivers (83.3%, n=85) knew the diagnosis of their patients while 15.7% did not know. The most common diagnoses were breast cancer with 9.8% (n=10), then colon with 4.5% (n=5) and following cancer types with decreasing frequency: stomach, ovary, lung, liver, and testicular cancers. A group of caregivers (6.9%) had cancer-diagnosed relatives other than the current patient.

According to the questionnaires delivered to identify the frequency of depression in caregivers of cancer patients, the risk for depression was identified as 43.1% (n=44) according to the BAS, and as 91.2% (n=93) according to the HADS. The anxiety rate was 66.7% (n=68) according to the BAS. Among these, 36.7% (n=25) demonstrated mild anxiety, 30.8% (n=21) demonstrated moderate anxiety, and 32.3% (n=22) demonstrated severe anxiety. According to HADS, the risk for anxiety was 72.5% (n=74).

As a result of the analysis, no significant differences were found between the caregivers' depression status and all other variables such as gender, educational status, monthly income, marital status, the degree of proximity to the patient, knowing the diagnosis, and knowing another cancer patients in terms of BDS results. There was no significant difference between anxiety level and other variables in the light of BAS results whereas a significant relationship between the gender of caregivers and anxiety level (p=0.041) was determined.

After the detailed analysis of scale questions in terms of BAS results, a strong relationship has been detected between depression status and some other symptoms such as thought of not being able to relax (p=0.013), dizziness/vertigo (p=0.013), feeling of horror (p=0.006), sense of irritability (p=0.003), fear of losing control (p=0.001), sense of fear (p=0.001), dyspepsia (p=0.009), and feeling of faintness (p=0.044).

Discussion

High incidence of depression has been reported among cancer caregivers in various scientific studies performed both in the world and in Turkey. An increase in depressive and anxious findings was observed in the palliative care group, regardless of whether the caregivers were from family or professional health care workers. Having a palliative care patient is strongly related to mood state, daily quality of life, and sleep quality [8-13]. Many scientific studies have questioned the depressive mood status by using BDS. Depression status of caregivers in our study was assessed by HADS in addition to the BDS. The frequency of depression in HADS was found higher, depending on the questions included in the surveys. It is understood that it will be essential to apply both scales to assess caregivers' emotional states. BAS and HADS scales were also employed in our study to determine the anxiety status of caregivers. Many studies have focused only on the depressive mood of caregivers; however, we thought that the effects of anxiety, as well as depressive mood on the caregivers, were also of interest.

The HAD scale was used in a study performed in a regional cancer center in Ontario-Canada on a group of breast cancer patients and 89 educated health care providers. During the three-year period, both patients and caregivers were more depressed at similar rates (11% and 12% respectively). The notable finding in the mentioned study is that anxiety rates were found higher in caregivers than in patients (35% and 19%, respectively) (p=0.009) [9]. The rates obtained from our study were relatively high.

A study performed by Çivi et al. and focused on the factors affecting depression and quality of life in caregivers of cancer patients reported similar results with our research by using BDS. According to the study results, 65.5% of the caregivers were normal, whereas 24.5% had mild, 7.3% moderate, and 2.7% severe depression. The gender, occupation, education, and marital status of the caregivers did not affect the depressive condition (p>0.05) [10]. In another study, the HAD scale was applied to 33 cancer patients and 33 caregivers. Anxiety and depression were detected as 76% among patients and caregivers and among those who knew their diagnosis at the 2/3rd of the chemotherapy treatment, mild anxiety and

depression were detected in 26% [14]. According to the data, it has been discovered that it is important to provide training, close follow-up and psychological support to the patients and their caregivers.

A study performed by Karabulutlu et al., which included 150 caregivers reported that 46% of the caregivers had anxiety and 72% of them had a depression risk [11]. The frequency of anxiety and depression of the mentioned study is parallel to our study. Grov et al. aimed to find out the relationship between SF-36 quality-of-life questionnaire and HADS in 49 female with breast cancer and 47 male with prostate cancer in their study. They reported that anxiety was found in both genders with equal rates and excess density, while no significant difference was detected regarding depression level. According to the HADS, depression rate is significantly more in female caregivers than the normal female population [13]. There was no significant difference in depression rates between both genders in our study.

Young Sun Rhee et al. investigated the effects of emotional burden on depression in 310 cancer caregivers and used BDS scale as well as the quality-of-life scale of cancer caregivers. They observed high levels of depression in 67% of caregivers and very high levels in 35% [15]. Depression frequency obtained from the mentioned study was nearly similar to the frequency of our research obtained with HADS.

Sarı et al. used the Pittsburgh Sleep Quality Index (PSQI) and the BDS questionnaires in 102 cancer caregivers. The vast majority of caregivers stated that they had a sleeping problem (85.3%) and 40.2% of them were experiencing symptoms of depression [16]. The depression symptom percentage of the mentioned study (40.2%) was almost the same as our percentage (43.1%). Cipolletta et al. compared the dependency scales of BAS and BDS in 50 cancer caregivers. Three different profiles about how caretakers use their facilities to give and/or get help were determined by this study. The obtained data has shown that if the status of providing support and experience and personality traits of caregivers are compatible, the anxiety and depression levels decreased; otherwise their levels increased. [17]. One possible limitation of our study may be related to the dependency of the variables.

Conclusion

The fact that the presence of depression and anxiety was significant in the caregivers of patients in the palliative care service warrants careful follow-up and necessary support of both the patients and their caregivers for mood disorders.

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Original Article

Evaluation of mean platelet volume and platelet count in patients with schizophrenia

Şizofreni hastalarında ortalama trombosit hacminin değerlendirilmesi

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ABSTRACT

Introduction: Compared to the general population, cardiovascular diseases are more common in schizophrenia patients and the mortality rate is higher than the general population. One of the explanations for increased cardiovascular events in patients with schizophrenia is the increase in platelet activity. Platelets are essential for progression of atherosclerotic lesions, plaque destabilization, and thrombus formation. Mean platelet volume (MPV) is a measure of platelet size and a good marker of platelet function and activation, which increases in cardiovascular diseases. MPV is routinely reported during complete blood count analysis. The aim of the present study was to evaluate MPV values of patients with schizophrenia.

Methods: In this retrospective study, hospital-records of the patients who were consecutively admitted to psychiatry inpatient clinic between January 2015 and January 2017 with the diagnosis of schizophrenia were reviewed. Healthy subjects with no personal history of psychiatric disorder were included as a control group.

Results: A total of 100 (59 female, 41 male) schizophrenic patients who had been consecutively admitted to the psychiatry inpatient clinic and 37 (20 female, 17 male) healthy controls were included in this retrospective study. There were no significant differences between the patient group and control group in the terms of age (mean age patient group vs control group: 37.72 vs 35.03, p=0.081) and sex (p=0.603). Body mass index (BMI) was found to be significantly different between groups, higher in the patient group (p=0.001). The MPV was found to be significantly higher in patient group compared with the control group (MPV, patient group vs control group: 10.34 fL vs 9.97 fL, p=0.041). Platelet count (PC) was significantly lower in the patient group (PC, patient group vs control group: 234.36 vs 267.38, p=0.008) There was no correlation between MPV and BMI (p=0.354, r=0.10), and duration of illness (p=0.530, r=0.06).

Conclusions: As a result, increased MPV and decreased PC were found in a group of schizophrenic patient in this study. Since increased MPV and decreased PC are evaluated as risk factors for cardiovascular diseases in the general population, they can also be considered as a predictor of risk factors for cardiovascular diseases that are more frequently encountered in schizophrenia.

Keywords: Cardiovascular diseases, mean platelet volume, schizophrenia

ÖZ

Giriş: Şizofreni hastalarında genel popülasyona kıyasla kardiyovasküler hastalıklara daha sık rastlanmaktadır, mortalite oranı genel popülasyona göre daha yüksektir. Şizofreni hastalarında artmış kardiyovasküler olayların açıklamalarından biri de trombosit aktivitesinin artmasıdır. Trombositler aterosklerotik lezyonların progresyonu, plak destabilizasyonu ve tromboz oluşumu için gereklidir. Ortalama trombosit hacmi (MPV), trombosit büyüklüğünün ve kardiyovasküler hastalıklarda artan platelet fonksiyonunun ve aktivasyonunun iyi bir göstergesidir. Tam kan sayımı analizi sırasında MPV rutin olarak bakılmaktadır. Bu çalışmanın amacı şizofreni hastalarının MPV değerlerini değerlendirmektir.

Yöntem: Bu retrospektif çalışmada psikiyatri kliniğine Ocak 2015 – Ocak 2017 tarihleri arasında ardışık olarak başvurmuş olan şizofreni hastalarının hastane dosya kayıtları incelendi. Kişisel psikiyatrik öyküsü olmayan sağlıklı bireyler kontrol grubu olarak alındı.

Bulgular: Psikiyatri polikliniğine ardışık olarak başvuran toplam 100 (59 kadın, 41erkek) şizofreni hastası ve 37 (20 kadın, 17 erkek) sağlıklı kontrol bu retrospektif çalışmaya alındı. Hasta grubu ve sağlıklı kontrol grubu arasında yaş (hasta grubu ve kontrol grubu ortalama yaş, sırasıyla 37,72 ve 35,03, p=0,081) ve cinsiyet bakımından anlamlı bir fark yoktu (p=0,603). Vücut kitle indexi (VKİ) hasta grubunda daha yüksek olmasıyla gruplar arasında anlamlı fark bulunmuştur (p=0,001). MPV kontrol grubuna kıyasla hasta grubunda anlamlı yüksek bulundu (hasta grubu ile kontrol grubu MPV sırayla; 10,34 fL ve 9,97 fL, p=0,041). Platelet sayısı (PC) hasta grubunda anlamlı düşük bulundu (hasta grubu ile kontrol grubu platelet sayısı sırayla: 234,36 ve 267,38, p=0,008). MPV ve VKİ arasında herhangi bir ilişki bulunmadı (p=0,354, r=0,10), MPV ile hastalık süresi arasında herhangi bir ilişki bulunmadı (p=0,530, r=0,06).

Sonuç: Sonuç olarak, bu çalışmada bir grup şizofreni hastasında artmış MPV ve azalmış PC bulundu. Artmış MPV ve azalmış PC, genel popülasyonda kardiyovasküler hastalıklar için risk faktörü olarak değerlendirildiğinden, şizofrenide daha sık karşılaşılan kardiyovasküler hastalıklar için risk faktörlerinin bir göstergesi olarak da düşünülebilir.

Anahtar kelimeler: Kardiyovasküler hastalıklar, ortalama trombosit hacmi, şizofreni

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Introduction

Schizophrenia is a progressive, chronic and devastating mental disorder characterized by psychotic symptoms such as hallucinations, delusions, and cognitive symptoms that affect almost all aspects of mental activity, including perception, attention, memory, and emotion [1]. Cardiovascular diseases are more common in schizophrenia patients than the general population, and mortality rate is higher than the general population [2]. The increase in platelet activity is an explanation of increased cardiovascular events in schizophrenia patients [3, 4]. Platelets are small, anucleotide cytoplasmic cells without genomic DNA, and they play essential roles in the progression of atherosclerotic lesions, plaque destabilization, and thrombus formation by releasing mediators for coagulation, inflammation, and atherosclerosis [5, 6]. Platelet activation including change in platelet shape, platelet aggregation and the release of platelet constituents has been associated with the pathogenesis of a number of diseases, which include atherosclerosis, coronary vascular disease, cerebrovascular disease, and also neuropsychiatric disorders [7, 8].

Mean platelet volume (MPV) is a measure of platelet size and a good marker of platelet function and activation [8]. Increased MPV levels are accepted as an indication of increased platelet activity [7]. Studies show that increased MPV is an independent risk factor for cardiovascular and atherosclerotic diseases [9, 10]. MPV has been found to be elevated in various mental disorders. The relationship between anxiety disorders, bipolar disorder, schizophrenia, major depression and increased platelet activity has been reported by several studies [11-15].

The platelet count has been used as a platelet concentration parameter. Platelet concentration is crucial for the maintenance of hemostatic function [16]. Low platelet concentration indicating decrease in platelet count can be observed in numerous cases including increased peripheral platelet destruction, increased splenic sequestration, decreased bone marrow platelet production [17]. The relationship between MPV and PC is unclear [18]. Several studies report an inverse association between platelet volume and number of platelet while a few study reports both increase during cardiovascular events [17, 19-21].

The aim of the present study was to evaluate MPV values and platelet count (PC) of patients with schizophrenia, and support the recent studies about using platelet parameters as an alternative strategy to monitor for cardiovascular diseases in schizophrenic patients.

Methods

This retrospective study included 132 consecutive patients at the age of 18-65 who were admitted to psychiatry inpatient clinic of Konya Training and Research Hospital with the diagnosis of schizophrenia and fullfilled the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) criteria between January 2015 and January 2017. Data from 100 (59 female, 41 male) patients were finally analyzed after excluding 32 patients with missing data. The control group consisted of 37 (20 female, 17 male) age and gender matched healthy volunteers with no personal history of psychiatric disorder. The study protocol was approved by the Institutional Review Board of Selcuk University Faculty of Medicine, Konya and adhered to the tenets of the Declaration of Helsinki (24.05.2017; 2017/163). Informed consent was obtained from all subjects prior to their participation in the study.

Criteria for the exclusion of a subject from the study were as follows; (1) coronary artery disease/myocardial infarction/heart valve disease, (2) pulmonary disease, (3) rheumatic disease, (4) liver disease, (5) neurological deficit/mental retardation/autism, (6) iron deficiency anemia, (7) pregnancy, (8) infection, (9) kidney disease, (10) alcohol/substance use, (11) antiplatelet-anticoagulant drug use, (12) bone marrow disease/myelodysplastic syndrome.

Sociodemographic and Clinical Data Form: Semi-structured sociodemographic and clinical data form was developed by the researchers of the study. Medical records including patient socio-demographic, clinical variables and complete blood count analysis, and reports from relatives and/or caregivers used as information sources.

Statistical analyses

Statistical analysis was performed using Statistical Package for Social Sciences (SPSS) 20.0 for Windows (SPSS, Inc., Chicago, IL, USA). Descriptive parameters are expressed as mean, standard deviation or percentage. Once the normality of the data was determined via Kolmogorov Smirnov test; two-sided t-test and Pearson Chi-square test were used for comparison of normally distributed variables of patients with schizophrenina and healthy volunteers. Abnormal distributed variables were compared with Mann–Whitney U-test. While investigating the associations between MPV and other variables, correlation coefficients and their significance were calculated using Pearson test. For all evaluations, a p value of less than 0.05 was considered as statistically significant.

Results

Data of 100 (59 female, 41 male) patients with schizophrenia and 37 (20 female, 17 male) healty control were analyzed in this study. The ratio of females was 59.00% in the schizophrenia group and 54.10 % in the control group. There were no significant differences between the patient group and control group in the terms of age (mean age patient group vs control group: 37.72 vs 35.03, p=0.081) and sex (p=0.603). Body mass index (BMI) was found to be significantly different between groups, higher in the patient group (p=0.001). Sociodemographic and clinical characteristics of the patient and control groups are given in Table 1.

Table 1. Characteristics of patients with schizophrenia and the control group participants

Characteristics	Schizophrenia (n=100), (%), ±SD	Control (n=37), (%), ±SD	*p value*
Sex			
Female, n (%)	59 (59.00%)	20 (54.10%)	0.603
Male, n (%)	41 (41.00%)	17 (45.90%)	
Age	37.72±9.42	35.03±7.28	0.081
Duration of illness, years	13.56±8.05	_	
BMI	29.02±7.48	25.34±4.37	**0.001**

Values are mean n: number; ± SD: Standard Deviation; Bold values indicate statistical significance; BMI: Body Mass Index

Ninety-seven (97.00 %) patients were on antipsychotic treatments. Forty-five patients were treated with depot antipsychotics as monotherapy, 15 patients were treated with oral antipsychotics as monotherapy, 37 patients were treated with both depot and oral antipsychotics as combination therapy and 3 patients were drug naïve on admission. There were no significant differences between the monotherapy group and combination therapy group in the terms of MPV (mean MPV monotherapy group vs combination therapy group: 10.34 vs 10.38, p=0.834) and PC (mean PC monotherapy group vs combination therapy group: 240.43 vs 226.79, p=0.305). There were no significant differences between the typical depot antipsychotics as monotherapy group (n=19) and atypical depot antipsychotics as monotherapy group (n=26) in the terms of MPV (mean MPV typical depot antipsychotics monotherapy group vs atypical depot antipsychotics group: 10.44 vs 10.40, p=0.893), and PC (mean PC typical depot antipsychotics monotherapy group vs atypical depot antipsychotics monotherapy group: 231.16 vs 250.00, p=0.405) (Table 2).

Table 2. Mean platelet volume and platelet count in patients with schizophrenia according to typical or atypical depot antipsychotic monotherapy

Parameters	Typical Depot Antipsychotics Monotherapy (n=19) ±SD	Atypical Depot Antipsychotics Monotherapy (n=26) ±SD	*p* value
MPV (fL)	10.44±0.99	10.40±1.00	0.893
PC (K/uL)	231.16±72.20	250.0±75.61	0.405

Values are mean n: number; ± SD: Standard Deviation; MPV: Mean Platelet Volume; PC: Platelet Count;

According to the comparison of blood count values, MPV was found to be significantly higher (MPV patient group vs control group: 10.34 fL vs 9.97 fL p=0.041), and PC was significantly lower (PC patient group vs control group: 234.36 vs 267.38, p=0.008) in the schizophrenina group. The laboratory findings for the two study groups are presented in Table 3.

Table 3. Laboratory findings for the patients with schizophrenia and control group participants

Parameters	Schizophrenia (n=100), ±SD	Control (n=37), ±SD	*p value*
MPV (fL)	10.34±0.93	9.97±0.97	**0.041**
PC (K/uL)	234.36±63.48	267.38±65.92	**0.008**
Cholesterol	190.10±44.99	195.97±42.54	0.493
AST	19.59±7.80	20.57±7.45	0.510
ALT	17.56±12.93	21.32±11.85	0.124

Values are mean n: number; ± SD: Standard Deviation; Bold values indicate statistical significance; MPV: Mean Platelet Volume; PC: Platelet Count; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase

There was no correlation between MPV and BMI in the patient group (p=0.354, r=0.10), and in the control group (p=0.273, r=0.2). There was no correlation between MPV and duration of illness in the patient group (p=0.530, r=0.06). Also, there was no correlation between MPV and age in the patient group (p=0.398, r=-0.08).

When patients with schizophrenia were evaluated according to sex, PC was significantly higher in females than in males (PC female group vs male group: 245.12 vs 218.88, p=0.041). However, there were no statistically significant differences in terms of MPV (p=0.190) (Table 4).

Table 4. Mean platelet volume and platelet count in patients with schizophrenia according to sex

Parameters	Female (n=59) ± SD	Male (n=41) ± SD	*p* value
MPV (fL)	10.24±0.88	10.49±0.99	0.190
PC (K/uL)	245.12±62.83	218.88±61.91	**0.041**

Values are mean n: number; ± SD: Standard Deviation; Bold values indicate statistical significance; MPV: Mean Platelet Volume; PC: Platelet Count

Discussion

The present study found higher MPV levels and lower PC in a group of patients with schizophrenia when compared with the healthy controls. Patients with schizophrenia are reported to be at higher risk for cardiovascular diseases, and they have shorter life spans than the general population [2, 22]. Although several risk factors such as genetic vulnerability, smoking, lifestyle factors including an unhealthy diet, lack of exercise, and treatment with antipsychotic drugs have been identified for the association between schizophrenia and cardiovascular diseases, the exact mechanisms that increase cardiometabolic risk factors and metabolic syndrome in schizophrenic patients remain unclear [22-25].

Platelets play an important role in cardiovascular diseases. The increase in platelet activity is one of the explanations proposed for increased cardiovascular events in schizophrenic patients [3, 4]. MPV has been used as a peripheral marker of platelet activity, and increased MPV levels are accepted as an indication of increased platelet activity [7]. The relationship between schizophrenia and increased platelet activity has been previously reported by several studies. Our study results showing an increase in MPV and a decrease in PC in schizophrenia are consistent with previous studies. One of these studies, by Semiz et al., assessed the effect of treatment with antipsychotics on platelet volume [26]. They found significantly higher MPV levels in patients who were on atypical antipsychotic drugs than in patients who were not using any drug and also higher than control group. Furthermore, they reported that patients who were not using antipsychotics had higher MPV than control group. Semiz et al concluded that MPV appears to be affected not only by schizophrenia itself but also by atypical antipsychotic medications.

In another study, by Wysokiński and Szczepocka, which assessed the platelet parameters in patients with schizophrenia, unipolar depression and bipolar disorder found significant differences in platelet parameters between study groups. Patients with schizophrenia had significantly higher MPV levels and had significantly lower PC than other study groups [12]. Wysokiński and Szczepocka have also analyzed differences in platelet parameters between sex and age-subgroups. They found significant sex and age differences for PC and MPV in schizophrenia patients. Our results does not include analyzes comparing sex and age sub-groups. Investigating the associations between age, sex and platelet-releated parameters may help understanding the increased risk better for cardiovascular diseases in psychiatric disorders.

Lee et al. revealed that increase in MPV were found to be independent of antipsychotic treatment in their study. They concluded that there were no differences between antipsychotic types, and the MPV and PC were not significantly altered after 1 year of clozapine treatment [11]. In our study, we also compared patients receiving typical depot antipsychotic medications with atypical depot antipsychotic medications as monotherapy in order to investigate whether the changes in platelet parameters was due to typical or atypical antipsychotic therapies. Concordant with study reported by Lee et al., we found no significant differences between the typical and atypical depot antipsychotic medication group in the terms of MPV and PC. These results indicate that increase in MPV and decrease PC in schizophrenia might be related to the underlying disease process.

Body mass index is reported to have an increasing effect on MPV levels [27]. Coban et al. aimed to evaluate the effect of weight loss on the MPV in obese patients. The results of this study indicated that MPV levels decreased after a three month diet treatment in the obese group. They found a positive correlation between weight loss and reduction in MPV. We compared BMI of patients with schizophrenia with healthy controls. BMI was found to be significantly different between groups, higher in the patient group. Although there was no correlation between MPV and BMI in the patient group and in the control group, elevation in MPV levels in schizophrenia group may be attributed to higher BMI of patient group.

A number of limitations should be considered for our study. The heterogeneity of patients in terms of disease progression (i.e. acute/chronic), in terms of symptom severity and in terms of treatments received (i.e. type of antipsychotics, antidepressants etc.) are some of the limitations that make it difficult to generalize the results to all sub-groups.

Conclusion

In conclusion, the measurement of platelet volume and activity is thought to be a predictor of cardiovascular disease in the general population, and may be used as an alternative strategy to monitor for cardiovascular diseases in schizophrenic patients. The mechanism underlying the differences in platelet-related parameters is still not understood. There is need for further studies establishing the association of platelet activity and platelet-related parameters with cardiovascular diseases in patients with schizophrenia and other psychotic disorders.

Preliminary results of this study were presented in oral sessions in “9th International Congress on Psychopharmacology & 5th International Symposium on Child and Adolescent Psychopharmacology”

Conflict of Interest: None.

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