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Cerebral Sinus Venous Thrombosis: Evaluation of Nineteen Patients

Serebral Sinüs Ven Trombozu: On Dokuz Hastanın Değerlendirilmesi

Zeynep Özözen Ayas[1], Ruhsen Öncel Öcal[2], Ayhan Bölük[1]

[1]Sakarya University Training and Research Hospital, Clinic of Neurology, Sakarya, Turkey
[2]Başkent University Hospital, Clinic of Neurology, Ankara, Turkey

Abstract

Objective: Cerebral sinus venous thrombosis (CSVT) is a disease that can be seen in all age groups with various clinical findings and usually a good prognosis. In this study, evaluation of the complaints on admission, the possible risk factors, localization, findings and treatment approaches, and discussion of these findings with comparison to the literature were aimed.

Materials and Methods: The demographic, clinical, laboratory and the radiological characteristics of 19 patients with diagnosed with CSVT and followed at the Sakarya University Training and Research Hospital Clinic of Neurology.

Results: Nineteen patients (15 female, 4 male) with the diagnosis of CSVT were included. The mean age of the patients was determined as 31.3±11.2. Headache was determined to be the first symptom on admission in 17 patients. Nausea-vomiting (n=10), blurred vision (n=4) and epileptic seizures (n=3) had accompanied headache. Altered state of consciousness (n=2), papilledema (n=4), dysarthria (n=1), and cerebellar disorder (n=1) were determined. Two of the patients were pregnant and 6 patients were in the postpartum period. CSVT due to infection was determined in 2 patients. No reason for etiological investigation was found in 4 of the cases. In 11 patients, more than one etiology were detected. Two patients had been diagnosed with Behçet's disease. *MTHFR A1298C* gene heterozygous mutation was most detected. Fourteen patients were determined to have a single sinus venous thrombosis and 5 patients had more than one sinus venous thrombosis on magnetic resonance venography. Six patients had venous infarction.

Conclusion: Pregnancy and postpartum period are significant risk factors for CSVT. The association of more than one reason in the etiological investigations of patients despite the presence of one significant risk factor has been emphasized.

Keywords
Cerebral sinus venous thrombosis, symptoms, etiological factors

Anahtar Kelimeler
Serebral sinüs ven trombozu, semptomlar, etiyolojik faktörler

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Address for Correspondence/Yazışma Adresi:
Zeynep Özözen Ayas MD,
Sakarya University Training and Research Hospital, Clinic of Neurology, Sakarya, Turkey
Phone : +90 505 903 95 05
E-mail : zozozen@hotmail.com
ORCID ID: orcid.org/0000-0002-9302-5543

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Öz

Amaç: Serebral sinüs venöz trombozu (SSVT) her yaş grubunda rastlanılabilen, çok çeşitli klinik bulgulara ve genellikle iyi prognoza sahip bir hastalıktır. Bu çalışmada hastaların başvuru şikayetleri, olası risk faktörleri, lokalizasyonu, bulguları ve tedavi yaklaşımlarımızın ortaya konulması ve bulgularımızın literatürle tartışılması amaçlanmıştır.

Gereç ve Yöntemler: Sakarya Üniversitesi Eğitim ve Araştırma Hastanesi Nöroloji Kliniği'nde SSVT tanısı alarak izlenmiş olan 19 hastanın demografik, klinik, laboratuvar ve radyolojik özellikleri değerlendirilmiştir.

Bulgular: SSVT tanısı alan 19 hasta (15 kadın, 4 erkek) alındı. Hastaların yaş ortalamaları 31,3±11,2 idi. Baş ağrısı 17 hastada ilk başvuru şikayeti olarak saptandı.

Baş ağrısına bulantı-kusma (n=10), bulanık görme (n=4), epileptik nöbet geçirme (n=3) eşlik ediyordu. Bilinç bulanıklığı (n=2), papil ödem (n=4), dizartri (n=1), serebellar bozukluk (n=1) tespit edildi. Hastalardan 2'si gebe, 6'sı postpartum dönemde idi. İki hastada enfeksiyona bağlı SSVT saptandı. Dört hastada etiyolojik araştırmada bir neden bulunamadı. On bir hastada birden fazla etiyoloji saptandı. İki hastaya Behçet hastalığı tanısı kondu. En fazla *MTHFR A1298C* heterozigot gen mutasyonu saptandı. Manyetik rezonans venografide 14 hastada tek, 5 hastada birden fazla sinüste venöz tromboz saptandı. Altı hastada venöz enfarkt saptandı.
Sonuç: Gebelik ve postpartum dönem SSVT için önemli risk faktörleridir. Hastaların etiyolojik araştırmasında belirgin risk faktörü varlığında bile birden çok nedenin birlikteliği vurgulanmıştır.

Introduction

Cerebral sinus venous thrombosis (CSVT) is a disease that can be seen in all age groups with various clinical findings and usually a good prognosis. It comprises around 0.5% of all causes of cerebrovascular stroke (1). Despite the disease being observed at all age groups, it is more commonly seen in adult females. The most important known etiologies are pregnancy and the postpartum period, oral contraceptives (OCPs), systemic inflammatory diseases, malignancy, infections, coagulation disorders and hematological diseases. The diagnosis and the awareness about the disease, which usually has a good prognosis, have increased because of advanced imaging techniques.

Materials and Methods

The clinical and the radiological characteristics of 19 patients admitted to the Sakarya University Training and Research Hospital Clinic of Neurology and the Adult Emergency Service and treated in the neurology ward with the diagnosis of cerebral venous thrombosis (CVT) between 2011 and 2014 were evaluated in this study. The demographic, clinical, laboratory and the radiological findings of the patients were investigated. In this study, evaluation of the complaints on admission, the risk factors, localization of CSVT, findings and treatment approaches, and discussion of these findings with comparison to the literature were aimed. Vitamin B12, folic acid, thyroid stimulating hormone and the C-reactive protein levels of the patients, in addition to routine laboratory tests, were recorded. Homocysteine (HS), anti-nuclear antibody (ANA), anti-cardiolipin antibody (ACA), fibrinogen, active protein C resistance (APCR), anti-thrombin III (AT III), protein C (PC), protein S (PS), factor V Leiden (*FVL*) mutation, prothrombin gene *G20210A* mutation (*Prt* G2021A), methylene tetrahydrofolate reductase (MTHFR) *C677T* and *A1298C* gene mutations were analyzed in most of the cases where possible. The diagnosis of the disease was established according to the cranial magnetic resonance imaging (MRI) and cranial MRI venography, and the patients who were investigated with these imaging techniques were included for the evaluation. All procedures performed in studies involving human were in accordance with the ethical standards of Sakarya University Training and Research Hospital at which the studies were conducted (approval no: 71522473/050.01.04/66). Informed consent was obtained from the patients.

Results

A total number of 19 patients with the diagnosis of CSVT were included in the study. Table 1 presents the main characteristics of the patients. Fifteen of the patients were female and 4 were male. The mean age of the patients was determined as 31.3±11.2, while the mean age of the female patients was determined as 30.7±11.1.

Headache was determined to be the complaint on admission in 17 (89.4%) patients. Ten of the cases that had presented with headache also had a history of nausea-vomiting, 4 had blurred vision and 3 had epileptic seizures. In addition, 1 patient had speech difficulty and 1 patient was admitted with the complaints of right-sided weakness, numbness and epileptic seizures. Altered state of consciousness was determined in 2 (10.5%) of the patients during the first examination. Furthermore, 4 (21.1%) patients had papilledema, 1 (5.3%) patient had dysarthria, and 1 (5.3%) patient had cerebellar disorder. Two (10.5%) of the patients were pregnant and 6 (31.6%) patients were in the postpartum period. None of the patients reported OCPs intake. Malignancy, immune suppression and thrombotic disease were not seen in the history of the patients. Infectious CVT was determined in 2 (10.5%) patients, one of which had mastoiditis and the other had dental abscess. Iron deficiency anemia was observed in 4 (21.1%) patients. No etiological reason underlying the condition was

found in 4 (21.1%) of the cases. In 11 (57.9%) patients, more than one etiology were detected. Two (10.5%) patients had been diagnosed with Behçet's disease as a result of the etiological investigation. Also 6 (31.6%) patients had a history of smoking. Three (25%) of 12 patients undergoing investigation for ANA tested positive, while all 12 patients undergoing investigations for ACA tested negative. In the genetic analysis, 1 (6.7%) of 15 patients evaluated for *FVL* gene mutation were heterozygous, 2 (13.3%) of 15 patients evaluated for *Prt G20210A* gene mutation were heterozygous, 2 (13.3%) of 15 patients evaluated for *MTHFR* C677T gene mutation were heterozygous and 2 (13.3%) of them were homozygous; 7 (46.7%) of 15 cases evaluated for *MTHFR A1298C* gene mutation were heterozygous and 1 (6.7%) of them was homozygous. Three (21.4%) of 14 patients undergoing HS level testing were determined to have high levels of HS. Two of the patients determined to have hyperhomocysteinemia, also had accompanying *MTHFR A1298C* gene mutation. Two (15.4%) of 13 patients checked for PC and PS levels had PC deficiency and 3 (23.1%) of them were determined to have PS deficiency. AT III levels were found to be within the normal range in all 13 patients undergoing evaluation. Hyperfibrinogenemia was determined in 1 (11.1%) out of 9 patients evaluated for fibrinogen levels. The heterozygous form was determined in 2 (20%) out of 10 patients evaluated for APCR levels. The diagnosis of the disease was established by cranial MRI and MRI venography. Fourteen (73.7%) patients were determined to have a single sinus venous thrombosis and 5 (26.3%) patients had more than one sinus venous thromboses. Venous infarction was determined in 6 (31.6%) of the patients (Figure 1a-d).

Discussion

CSVT has been reported to be more common among females. Similarly, it was determined to be more common among female patients at a rate of

Table 1. Demographic and clinical features of patients

	Age	Sex	Symptom	Sinus involvement	Etiology
1	26	F	H	Single	Pregnant, PS def, MTFHRA homo
2	19	F	H	Single	Postpartum, MTHFRA hetero
3	18	F	H	Single	Postpartum
4	38	M	H-NV-BV	Single	MTHFRC homo, HS, ANA
5	24	F	H-NV-BV	Single	PC def, ANA, MTHFRA hetero, HS, hypofibrinogenemia
6	32	M	H	Single	MTHFRA+MTHFRC hetero
7	31	F	H	Single	Postpartum, PS def, ANA, MTHFRA hetero
8	57	F	H-NV-S	Single	-
9	19	F	H-NV-BV-AS	Multiple	Pregnant, IDA, PS def, Prt+MTFHRA hetero
10	32	F	H-BK-BV	Single	Infection, MTHFRC homo, IDA, HS
11	18	F	H-NV-S	Multiple	Postpartum, PC def, FVL+Prt+MTHFRC hetero
12	43	F	SD	Multiple	Infection, IDA, MTHFRA hetero
13	44	F	H	Single	MTHFR hetero
14	37	F	H-NV-AS	Single	-
15	46	M	H	Single	-
16	29	F	H-NV-N	Single	Postpartum, IDA
17	23	F	WN-S	Multiple	Postpartum
18	40	F	H-NV	Multiple	-
19	19	M	H-NV	Single	HS

H: Headache, NV: Nause-vomiting, BV: Blurred vision, S: Seizure, AS:Altered state of consciousness, WN: Weakness numbness, SD: Speech difficulty, IDA: Iron deficiency anemia, HS: Hyperhomocysteinemia, F: Female, M: Male

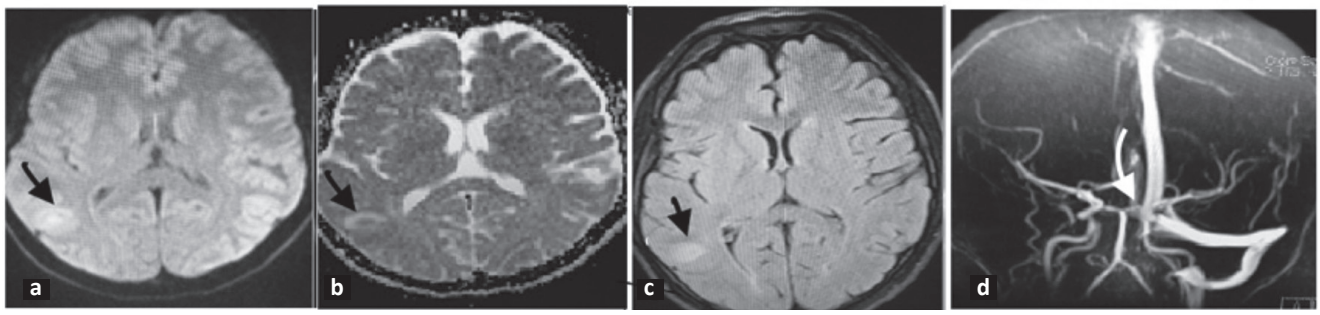

Figure 1. a, b) Diffusion, ADC magnetic resonance imaging showed that venous enfarkt on right occipital area, c) hyperintensity consistent with venous enfarkt on fluid-attenuated inversion recovery imaging, d) magnetic resonance venography showed occlusion of right transvers and sigmoid sinus

78.9% in our study. The study reported that the male/female ratio was reported as 1:1.29 (2). The age distribution among males has a homogenous distribution. However, the 20-35 years age range is more common at a rate of 61% in female patients. This type of age distribution is thought to be caused by pregnancy and OCP intake (3). The mean age was determined as 32±11.13 in a study evaluating 51 patients (4). Similarly, the mean age was calculated as 31.3±11.2 years in our study, and the mean age of the female patients was determined as 30.7±11.1 years. Headache is the most common presenting symptom of CSVT. In one study, headache was observed at a rate of 65.5% and it was seen at a rate of 80% in another study (5,6). Similarly, the complaint on admission was headache in 89.4% of the cases in our study. Headache is usually accompanied by another symptom. In our study, headache was also accompanied by other neurological findings in 64.7% of the cases. Chronic daily headache without any other neurological deficit was determined in 10.6% of the cases in a study evaluating 47 patients (6). Nausea and vomiting due to increased intracranial pressure can be accompanying symptoms. Nausea and vomiting were present in 58.9% of the cases complaining of headache. Seizures, hemiparesis and altered state of consciousness can be observed in the symptomatology. Four of our patients had seizures and altered state of consciousness was present in 2 patients. Wide different causes are among the etiologies of CSVT. In our study 10.5% (n=2) of cases were pregnant and 31.6% (n=6) were in the postpartum period. Pregnancy is an important prothrombotic state. Coagulation proteins such as von Willebrand factor, factor VIII, factor V and fibrinogen are increased, PS is decreased and APCR develops during pregnancy (7,8). In a study, it was shown that venous thromboembolism (VTE) increased by 10-fold during pregnancy (9). In our study, one case was in the first trimester and the other case was diagnosed with CSVT in the last trimester. The risk of CSVT is the same for all trimesters during pregnancy; however, the frequency is increased during the postpartum period (10,11). The postpartum period was determined to be the most common cause with 33.3% of the patients in one study (4). Furthermore, a 3 to 8-fold increased risk in the postpartum period compared to the period before delivery has been determined in the literature (12). More than almost half of the CSVT cases developing in the postpartum period occur without any other triggering causes in the 3rd-4th days after delivery. Six patients in our study were in the postpartum period and it was observed that the cases were diagnosed on the 5th, 7th, 20th, 40th, 60th and the 180th days postpartum. CSVT can develop during the course of systemic infections. In a case series including 14 cases of CSVT, 4 patients were determined to have infection (13). CSVT occurs frequently during bacterial and fungal diseases; however, it can be observed during parasitic and viral diseases as well. The frequency of thrombosis due to infectious causes such as sinusitis, otitis media and mastoiditis is decreased as a result of common antibiotic administration. Untreated dental abscess and mastoiditis were determined in 2 of our cases (10.5%). These cases were evaluated as infection-caused CSVT. Iron deficiency anemia is a rare cause of CSVT in adults. Secondary thrombocytosis, hypercoagulability due to increased viscosity and increased metabolic stress caused by iron deficiency anemia are suggested hypotheses. In one study, the

risk of developing CSVT was reported to be significantly higher in severe iron deficiency anemia patients compared to the control group (10). In our study, iron deficiency anemia was determined in 21.1% (n=4) of the cases. However, all these patients also either had pregnancy, were in the postpartum period, had infection or genetic mutations, and therefore, iron deficiency anemia-caused CSVT was not considered in any of these patients. *FVL* mutation is the most commonly seen genetic risk factor in VTE (3). The anticoagulation characteristic of APC is deteriorated by *FVL*, which is also called mutant factor, and the tendency towards thrombosis is increased (14). The *FVL* allele frequency in the general population is reported as 1-8%. The *FVL* gene mutation incidence was reported as 10% in a study including the Turkish population (15). Dentali et al. (16) reported *FVL* gene mutation as a risk factor contributing to the development of CSVT. Heterozygous *FVL* gene mutation increases the risk of thrombosis by 5-10 fold, while homozygous mutations increase this risk by 50-100 fold (14). In other studies, a significant relationship between *FVL* gene mutation and CVT was determined (17,18). In our study, *FVL* gene mutation was investigated in 15 patients and heterozygous mutation was determined in 1 case (6.7%). *Prt G20210A* mutation was shown to increase prothrombin levels in some studies, and to cause an increased risk of thrombosis by 2.7-3.8-fold and was reported as the second most common hereditary risk factor (14). The incidence of this mutation in patients diagnosed with CSVT has been reported as 11% and it is thought to cause a tendency towards thrombosis at higher rates than the *FVL* gene mutation alone (19). However, the estimated rate of this mutation for myocardial infarction, stroke or venous thrombosis was found as 1.05 in "The Physicians Health Study" evaluating 14916 cases prospectively (20). Heterozygous mutation was detected in 2 out of 15 patients (13.3%) investigated for *Prt G20210A* gene mutation. *MTHFR* gene polymorphisms (C677T, *A1298C*) presenting a risk factor alone or through HS levels is controversial. The incidence of these polymorphisms in healthy individuals has also been reported (21). In one study analyzing 376 cases, the prevalence of *MTHFR A1298C* mutation was reported to be higher than the prevalence of *MTHFR* C677T. They reported that 44.8% of the patients were normal, 42.3% were heterozygous mutant and 12.8% were homozygous mutant (21). According to the study conducted by Kluijtmans et al., (22) the *MTHFR* gene C677T variant shows a strong association with coronary artery diseases, peripheral artery diseases and venous thrombosis. The prevalence of homozygous mutant phenotype of *MTHFR* gene C677T variant has been reported as 5-9% in the Turkish population (23). In our study, 2 of 15 patients (13.3%) were determined to carry heterozygous and 2 were determined to carry (13.3%) homozygous *MTHFR* C677T mutation. 7 out of 15 (46.7%) patients investigated for *MTHFR A1298C* mutation were determined to have heterozygous and 1 of them to have a homozygous mutation. These mutations are clinically relevant if they cause hyperhomocysteinemia (24). In our study, associated homozygous *MTHFR A1298C* gene mutation was determined in 2 patients. PC, PS and AT III deficiency are known causes of VTE; however, its importance in CSVT is not certain (19). In our study, 2 (15.5%) patients were determined to have PC deficiency, and 3 (23.1%) patients to have PS deficiency, while all patients were found to have normal AT III levels among the 15 patients who were investigated for PC, PS, AT III levels. Reasons such as pregnancy, postpartum period and genetic mutations were present in PC- and PS-deficient patients. Association of more than one risk factor is important in the etiological investigations for CVT patients. Systemic investigation of each risk factor is important even in patients with one significant risk factor. Presence of more than one risk factor has been emphasized to increase the thrombosis risk significantly (25). In our study, the rate of patients with more than one etiology was determined as 57.9% (n=11). In International Study CVT (Study on Cerebral Vein and Dural Sinus Thrombosis), 44% of the cases were reported to have more than one reason, and 22% had hereditary thrombotic factors (26). Besides the variety in the etiology, no reason could be determined in 15% of the patients. No reason that could lead to CSVT was determined in 4 of our cases. ANA-positivity was determined in 3 patients as a result of vasculitis investigation and 1 of them was diagnosed with Behçet's disease at the end of 2-year follow-up. Another patient was diagnosed with Behçet's disease after the diagnosis of CSVT. CSVT is one of common neurological complications of Behçet's disease (25).

MRI and MRI venography are the first choice of investigation for the diagnosis of CSVT. All patients in our study were diagnosed with MRI and MRI venography. Six (31.6%) of our patients were determined to have venous infarction. The most frequently affected sinuses are the superior sagittal, transverse, sigmoid, cavernous and the sinus rectus, respectively. In a case series reported by Azin and Ashjazadeh (27) including 61 cases of CSVT, in 80.3% of the cases, the thrombosis was detected in the superior sagittal sinus; the sigmoid sinus was affected in 6.5% and cavernous sinus thrombosis was detected in 4.9%. However, transverse sinus involvement was the most common in our study with 15 patients. Other more common localizations are found in the literature. In another study, sigmoid sinus involvement was observed in 74.5% of 47 patients (6). Transverse sinus involvement was determined in another study including 13 CSVT cases (28). Involvement of more than one sinus was observed in 65.5% of the cases in one study and 31.1% was observed in another study (5,13). A rate of around 30% is observed for more than one sinus involvement. Anticoagulant therapy is the first choice (29,30). Recently developed new oral anticoagulant medications are being investigated for new options for treatment of CSVT (31). Very good improvement was observed in 87% of 15 patients receiving dabigatran and followed with detection of 80% recanalization (32). However, studies have been conducted with small numbers of patients and wider studies are required for higher efficiency (32,33). Anticoagulant treatment is our first choice despite the risk of increased hemorrhage, and 2 pregnant and 4 postpartum patients were treated with low molecular weight heparin and followed-up. CSVT has high morbidity and mortality if not diagnosed and treated early. 6-10% of the cases develop mortality despite adequate treatment (34). It was found that altered state of consciousness, hemorrhagic infarct, acute onset and hemiparesis were associated with an increased rate of mortality in a study including 47 CSVT patients (6). We did not have any cases resulting with mortality in our study. In present study.

Study Limitations

Our study also had a limitation about number of patients. Future prospective studies in large numbers of patients are needed to better describe features of CSVT patients.

Conclusion

Pregnancy and postpartum period are significant risk factors for CSVT. The association of more than one reason in the etiological investigations of patients despite the presence of one significant risk factor has been emphasized.

Ethics

Ethical Committee Approval: All procedures performed in studies involving human were in accordance with the ethical standards of Sakarya University Training and Research Hospital at which the studies were conducted (approval no: 71522473/050.01.04/66).

Informed Consent: Informed consent was obtained from the patients.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Z.Ö.A., R.Ö.Ö., A.B., Concept: Z.Ö.A.,R.Ö.Ö., A.B., Design: Z.Ö.A., R.Ö.Ö., A.B., Data Collection or Processing: Z.Ö.A., R.Ö.Ö., A.B., Analysis or Interpretation: Z.Ö.A., R.Ö.Ö., A.B., Literature Search: Z.Ö.A., R.Ö.Ö., A.B., Writing: Z.Ö.A., R.Ö.Ö., A.B.

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Original Article / Özgün Araştırma

Protective Effect of Pycnogenol® on Cisplatin Induced-Cardiotoxicity in Rats

Pycnogenol®'ün Sıçanlarda, Sisplatin ile İndüklenen Kardiyotoksisite Üzerine Koruyucu Etkisi

Ufuk Eryılmaz[1], Saliha Aksun[2], Buket Demirci[3]

[1]Adnan Menderes University Faculty of Medicine, Department of Cardiology, Aydın, Turkey
[2]Katip Çelebi University Faculty of Medicine, Department of Medical Biochemistry, İzmir, Turkey
[3]Adnan Menderes University Faculty of Medicine, Department of Medical Pharmacology, Aydın, Turkey

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Address for Correspondence/Yazışma Adresi:
Ufuk Eryılmaz MD,
Adnan Menderes University Faculty of Medicine, Department of Cardiology, Aydın, Turkey
Phone : +90 535 981 97 12
E-mail : drufukeryilmaz@gmail.com
ORCID ID: orcid.org/0000-0003-0287-8506

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Abstract

Objective: This study investigated the cardiotoxicity of cisplatin (CIS) on rat heart by using the oxidative damage of the rat myocardium, troponin I and serum S100A1 levels. Previous studies have reported that cell-protective effect of Pycnogenol® (PYC) depended on its antioxidant and anti-inflammatory properties. Hence, the myocardial protective effect of PYC was investigated in this study.

Materials and Methods: Rats were randomly grouped to four with 5 rats in each group. The groups were consisted of control group, PYC group: 10 mg/kg PYC for 7 days, CIS group: 15 mg/kg single injection of CIS on the 5th day, CIS + PYC group: 10 mg/kg PYC for 7 days, plus 15 mg/kg single injection of CIS on the 5th day. Heart and serum samples were acquired subsequently.

Results: CIS and PYC co-treatment group had increased catalase level (from 43.61±15.16 to 60.80±21.36, p<0.019) and prevented troponin I elevation (from 7.34±6.20 to 3.03±1.36). The S100A1 level was significantly reduced by CIS (from 10.25±8.8 to 3.99±2.87, p<0.035) and was restored by PYC treatment (32.07±29.23).

Conclusion: Injured cardiomyocytes released troponin I after exposure to CIS and PYC, which can protect the cells from CIS cardiotoxicity, increased the tissue catalase level. Additionally, PYC treatment increased serum level of S100A1.

Öz

Amaç: Bu çalışmada sıçan kalbi üzerinde sisplatin (CIS) kardiyotoksisitesi, sıçan miyokardı oksidatif hasarını, troponin I ve serum S100A1 düzeyleri kullanılarak araştırılmıştır. Önceki çalışmalar, Pycnogenol®'un (PYC) hücre koruyucu etkisinin antioksidan ve anti-enflamatuvar özelliklerine bağlı olduğunu bildirmiştir. Bu nedenle, bu çalışmada PYC'nin miyokardiyal koruyucu etkisi araştırılmıştır.

Gereç ve Yöntemler: Sıçanlar randomize olarak grup başına 5 olacak şekilde dört gruba ayrıldı. Kontrol grupları, PYC grubu: 10 mg/kg 7 gün boyunca intraperitoneal PYC, 5 gün intraperitoneal olarak sisplatinin 15 mg/kg tek doz enjeksiyonu, sisplatin + PYC grubu: 10 mg/kg PYC intraperitoneal olarak 7 gün boyunca, artı beşinci günde 15 mg/kg tek sisplatin enjeksiyonu. Kalp ve serum örnekleri 8. günde elde edildi.

Bulgular: CIS ve PYC eş-tedavi grubunda katalaz seviyesi artmış (43,61±15,16'dan 60,80±21,36'ya, p<0,019) ve troponin I yükselmesi (7,34±6,20'den 3,03±1,36'ya) engellenmiştir. S100A1 seviyesi, CIS ile anlamlı ölçüde azalmıştır. (10,25±8,8'den 3,99±2,87'ye, p<0,035) ve PYC tedavisi (32,07±29,23) ile düzeltilmiştir.

Sonuç: Sisplatin ve PYC'ye maruz bırakıldıktan sonra hasarlı kardiyomiyosit hücrelerinden troponin I salınır ve CIS kordiyotoksisitesinden koruyabilen doku katalaz seviyesi artar. Ek olarak, PYC tedavisi, S100A1 serum seviyesini arttırdı.

Introduction

Cisplatin (CIS) is an alkylating chemotherapeutic agent. It is first used by treating ovarian and testis cancers in 1978 (1). Today, CIS is used for the treatment of lung, larynx, oral cavity, oropharynx, salivary gland, germ cell tumors and lymphomas. Nephrotoxicity, neurotoxicity, ototoxicity, and cardiotoxicity are the known side effects of the drug (2). The most significant factors limiting its utilization are nephrotoxicity and cardiotoxicity that can occur acutely or cumulatively and by similar mechanisms (3).

Pycnogenol (PYC) is obtained from pine tree (Pinuspinaster) shell and includes water-soluble bioflavonoids. PYC is used for medical conditions associated with oxidative stress such as renal and hepatic toxicity, tinnitus and diabetes mellitus (4-6). It was shown to protect against daunorubicin-induced cardiotoxicity by its antioxidant effect (7). However, it is not known whether PYC is protective against CIS cardiotoxicity.

One-Way ANOVA was used for three or more group comparisons and the Tukey HSD test was used for multiple comparison tests. If the preconditions are not met, Kruskal Wallis and the Bonferroni-Dunn test from multiple comparison tests are used. Correlation analysis between two continuous variables was also used.

Cardiac injury has been evaluated by oxidative damage on CIS-induced heart tissue. While troponin I is a well-known marker of cardiac injury, S100A1 originates in cardiomyocytes (8) and it is not clear whether its expression correlates with troponin or can be useful as a new marker of cardio-oncology.

Several studies have been performed about the cardio protective effects of natural products and found as promising during the cancer chemotherapy (7,9). On the other hand, the natural product can behave as an adjuvant and might further increase the toxicity of antineoplastic medicine (10). Therefore, the aim of the study was to investigate the PYC's efficacy and safety on CIS induced cardiotoxicity.

Material and Methods

Animals and Experimental Design

Four 6-month-old male Wistar albino rats were acquired from the Animal Care and Research Unit of Adnan Menderes University (ADU, Aydın, Turkey). The experiments were done according to the ADU Animal Ethical Committee's approval. This study evaluated the remained heart tissue of another study about "the protective effects of PYC® on CIS ototoxicity" after taking the new approval from the Committee (64583101/2013/037) to decrease the animal number used in medical experiments. The experimental groups were as these:

The rats were weighed and after that they were randomly assigned to four groups with five rats in each group.

Control group: Physiologic serum was given intraperitoneally for seven days and this was the healthy group.

PYC group: PYC 10 mg/kg (gifted from Horpag Research Ltd Geneva, Switzerland) was given intraperitoneally for seven days, beginning from the first day. The dose was taken from a renal toxicity research (5).

CIS group: CIS 15 mg/kg single injection (Platinol®, Bristol-Myers Squibb, İstanbul, Turkey) was administered intraperitoneally on the 5th day of the study.

CIS+PYC group: PYC 10 mg/kg PYC was given intraperitoneally for seven days, beginning from the first day. Furthermore, 15 mg/kg single injection of CIS was administered intraperitoneally on the 5th day of the study.

On the 8th day of study, under the anesthesia of Ketamine (50 mg/kg) and Xylazine (5 mg/kg), the blood was withdrawn by cardiac puncture, and the hearts were taken out immediately.

Determination of Oxidant/Antioxidant Parameters in Heart Tissues

Preparation of tissue samples: Rat hearts were homogenized for 10 minutes at 8000 rpm using a homogenizator over ice after weighing and cold chaining in a 50 mM phosphate tamponade (pH=7.0) (Heidolph, Silentcruster M, Germany). After homogenization, they were centrifuged with a refrigerator at +4 °C for 10 minutes and supernatants were kept at -80 °C (Hermle, Z 400 K, Germany). Tissue homogenate protein results were obtained as mg/dL with Abbott urinary protein kit using an autoanalyzer (Architect, Abbott).

Catalase (CAT) Activity

Aebi method based on kinetic measurement was used for diagnosis of CAT (11). It is measured by the reaction which gives rise to water and oxygen from hydrogen peroxide H_2O_2.

$$2\,H_2O_2 \xrightarrow{\text{catalase}} 2\,H_2O + O_2$$

In this study, CAT activity was detected as a decrease in H_2O_2 concentration in a time at 240 nm in a spectrophotometric (Dynamica Halo DB-20s, UK) analysis. Homogenates were diluted to a 1:5 dilution with 50 mM phosphate tamponade (pH=7.0). 1.00 mL H_2O_2 solution (30 mM) was added to 2.00 mL homogenate, and absorbance changes were recorded at 240 nm with 15-second intervals. Same procedures were reduplicated with randomized samples and activity, baseline and 30-second absorbances were calculated. Activity unit was reported as a ratio of obtained values to tissue protein level in k/mg.

Determination of Troponin and S100A1 in Serum

The blood was centrifuged (Hettich Zentrifugen, Mikro 200 R, Tuttlingen, Germany) at 10000 rpm for 10 min at 4 °C and the serum kept at -80 °C until the analysis. Serum troponin I level was established with immunoassay on Advia Centaur CP (Siemens, Germany) autoanalyzer. Rat serum S100A1 levels were established by using rat protein S100A1 ELISA kit (Cusabio Biotech, China) and studied on automatic Elisa plate reader (Biotech ELx800, USA). The optical density of each well was established within 5 minutes using a micro plate reader set to 450 nm.

Statistical Analysis

The results of tests were given as the number of observations (n), mean ± standard deviation, median and %25-%75 percentage values. In the decision of which statistical method to apply in the comparison of the study groups, the results of the homogeneity (Levene's test) and normality tests (Shapiro Wilk) were used. Normally distributed and with homogeneous variances groups were compared independent three or more groups by Analysis of Variance. Multiple comparison tests, the Tukey HSD test was used. According to those tests results parametric test assumptions were not available for some variables, so the comparisons of three independent groups were performed by Kruskal-Wallis test. Multiple comparison tests, the adjusted Bonferroni-Dunn test were used. If the relationship between the two variables does not satisfy the parametric test prerequisites, the Spearman Rho correlation coefficient is used. Data were analyzed using SPPS 20 (IBM Corp. Released 2011; IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp.) Software. P<0.05 was used for statistical significance.

Results

Catalase Level in the Heart Tissue

PYC did not affect CAT activity on healthy tissue, and 15 mg/kg of CIS did not reduce CAT level when compared to the control group, but co-treatment of PYC and CIS significantly triggered the antioxidant CAT level up to 60.80±21.37 (Table 1).

Serum Troponin I and S100 A1 Level

Serum troponin I level of CIS group was found elevated in the serum, and PYC was found to prevent the elevation. S100A1 level highly increased after PYC treatment (Table 1). Heart tissue CAT level showed a

Table 1. Catalase activity in heart tissue and troponin I and S100A1 levels in the serum of all experimental groups

	Control		Pycnogenol (10 mg/kg)		Cisplatin (15 mg/kg)		Cisplatin (15 mg/kg/day) + Pycnogenol (10 mg/kg)		p
	$\bar{x}$ ± Sandard deviation (SD)	Median (25%-75% quartile)	$\bar{x}$ ± SD	Median (25%-75% quartile)	$\bar{x}$ ± SD	Median (25%-75% quartile)	$\bar{x}$ ± SD	Median (25%-75% quartile)	
Troponin I	1.14±0.52	1.02 (0.78-1.57)	2.19±0.71	2.51 (1.44-2.78)	7.34±6.2	3.9 (2.68-13.72)[a]	3.02±1.36	2.84 (1.87-4.37)	0.019*[₹]
S100A1	10.25±8.81	7.09 (3-20.78)	5.67±11.44	0.96 (0.01-13.68)	4±2.87[b]	4.43 (1.07-6.49)	32.07±29.23[b]	24 (9.34-62.87)	0.049*[ṁ]
CAT	38.18±8.17	34.19 (31.18-46.19)	32.67±3.83	34.68 (28.6-35.74)	43.61±15.15	35.44 (32.4-58.91)	60.8±21.37[b]	49.72 (42.05-76.24)	**0.035***

*p<0,05, [₹]Kruskal-Wallis test, [ṁ]One-Way ANOVA, [a]DifferentFrom Control Group (Bonferroni-Dunn Test), [b]DifferentFrom Control Group (Tukey HSD test), CAT: Catalase

positive correlation with serum S100A1 level; r=0.47 p=0.04. One is increasing, while the other is seen as an increasingly "moderate" statistically significant relationship (Figure 1).

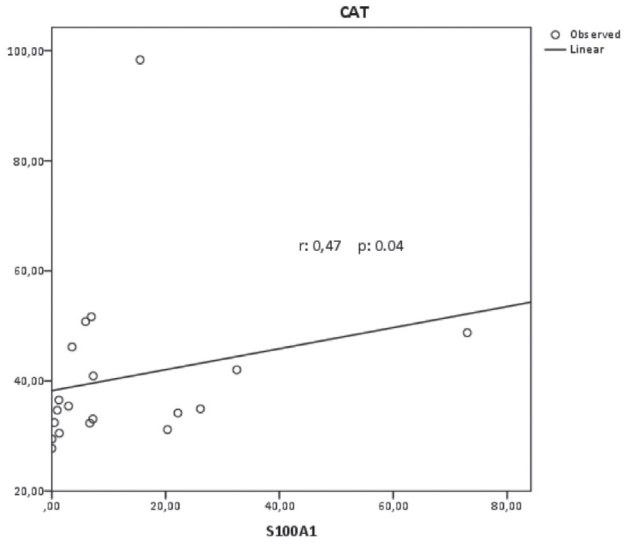

Figure 1. Correlation graph between the heart catalase activity and S100A1 level; r=0.47 p=0.04
CAT: Catalase

Discussion

In our study, it was found that PYC did not have any effect on CAT activity in healthy tissues and CIS did not lead to the reduction of the CAT level. However, when PYC and CIS were used together, they were found to trigger the antioxidant CAT level. The S100A1 value, which was found to be positively correlated with the CAT level in the heart tissue, also increased following PYC treatment. As expected, serum troponin I level was found elevated in CIS group, and when PYC was added to the treatment, this value was reduced due to the positive effect of PYC.

It might be expected that the adverse effects of drugs can be seen mostly in elimination organs such as liver and kidney. Moreover, the heart tissue is highly perfused; therefore, exposures to the drugs occur in high concentration. Due to technical problems, we were unable to assess the oxidant status such as the status of malondialdehyde (MDA) in the heart; however, El-Awady et al. (12) found that 10 mg/kg single dose of CIS significantly increased MDA level of heart tissue and proved that CIS is harmful to the heart tissue in animal study. Based on the tissue levels of CAT found in this study, the CIS 15 mg/kg was considered not to consume the CAT activity of the heart tissue severely; only troponin I level increased significantly as an early marker for cardiac injury. This increment was partially protected by PYC treatment together with increased CAT activity.

In addition to its antioxidant, anti-inflammatory, and antiplatelet effects, PYC was also shown to decrease oxidative stress and improve the function from the endothelium in coronary arterial diseases (13). Feng et al. (14) investigated the effect of PYC on cardiotoxicity in mice treated with antineoplastic drugs. In their study with the experimental mouse - doxorubicin model, they showed that PYC did not antagonize the effect of the antineoplastic agent. When administered at 150 and 200 mg/kg orally, PYC was found to prevent doxorubicin cardiotoxicity by inhibiting the elevation of creatine phosphokinase in the serum (14). The results related to levels of serum CAT and troponin I obtained in our rat model with CIS support this study. The CIS-related cardiac dysfunction is due to the disruption of the mitochondrial membrane as well as the ultrastructural abnormalities seen in mitochondria. It was shown that, following CIS treatment, the endoplasmic reticulum stress response and apoptosis were increased in cardiomyocytes (15). CIS was shown to lead to renal injury by triggering the formation of mitochondrial reactive oxygen species in renal tubular cells (16). Since toxicity occurs with a similar mechanism, the antioxidant treatment targeting mitochondria was reported to be protective against CIS-related cardiotoxicity and nephrotoxicity (17).

On the other hand, it was reported that S100A1 is rich in cardiomyocytes (8) and it is found in extracellular compartment following heart ischemia (18). The other member of S100 family, S100B protein expression was suggested as a new forensic marker for cocaine-induced heart injury (19). The crucial role of S100A1 for cardiac performance and contractility was reported (20,21). In our study, reduced release of S100A1 from injured cardiomyocytes to serum after CIS exposure was demonstrated, which was concordant with our previous study (22). Lapatinib and trastuzumab decreased S100A1 expression in a ratio of %75. In our study, we did not report any correlation between S100A1 and troponin I. Moreover, a positive correlation was found between S100A1 and CAT activity. A raised level of S100A1 due to the

concomitant application of PYC and CIS may give rise to the hypothesis of the beneficial effect of PYC together with anticancer drugs for decreasing cardiotoxicity. Studies using PYC to prevent cardiotoxicity in patients using cardiotoxic oncologic agents may be important in the future.

Conclusion

Single dose of CIS 15 mg/kg was enough to produce myocardial damage, as proven by troponin I level in this experimental rat model. We demonstrated that PYC treatment partially prevented the detrimental effect by increasing CAT activity which is in correlation with S100A1.

Acknowledgement: We wish to thank Horpag Research Ltd. (Geneva, Switzerland) for gifting us the Pycnogenol®.

Ethics

Ethics Committee Approval: Adnan Menderes University (ADU, Aydin, Turkey), Animal Ethical Committee (64583101/2013/037).

Informed Consent: Since it is an experiment on animals, there is no need for informed consent.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: B.D., S.A., Concept: U.E., B.D., Design: U.E., B.D., Data Collection or Processing: B.D., U.E., S.A., Analysis or Interpretation: U.E., B.D., S.A., Literature Search: U.E., B.D., Writing: U.E., B.D.

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Original Article / Özgün Araştırma

Effects of Intra-Articular Platelet-Rich Plasma Administration in Temporomandibular Joint Arthritis: An Experimental Study

Temporomandibüler Eklem Artritinde İntrartiküler Trombositten Zengin Plazma Kullanımının Etkisi: Sıçanlarda Deneysel Çalışma

Heval Selman Özkan[1], Saime İrkören[1], Huray Karaca[1], Taha Deniz Yıldırım[1], Kadir Çiçek[1], Canten Tataroğlu[2]

[1]Adnan Menderes University Faculty of Medicine, Department of Plastic and Reconstructive Surgery, Aydın, Turkey
[2]Adnan Menderes University Faculty of Medicine, Department of Pathology, Aydın, Turkey

Keywords
Temporomandibular joint, platelet rich plasma, osteoarthritis

Anahtar Kelimeler
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Address for Correspondence/Yazışma Adresi:
Heval Selman Özkan MD, Adnan Menderes University Faculty of Medicine, Department of Plastic and Reconstructive Surgery, Aydın,Turkey
Phone : +90 256 244 12 56
E-mail : selman_ozk@yahoo.com
ORCID ID: orcid.org/0000-0003-0345-5847

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Abstract

Objective: Osteoarthritis is defined as a disease that begins with focal and progressive destruction in articular cartilage with biomechanical, biochemical, inflammatory and immunologic reactions and may cause pathologic changes in the subchondral bone and joints. The platelet-rich plasma accelerates wound and bone healing in clinical trials; decreases swelling, pain, infection and scarring; and controls bleeding. In this study, we studied the effect of intraarticular thrombocyte-rich plasma administration in the model of temporomandibular osteoarthritis induced by monosodium iodoacetate (MAI) injection.

Materials and Methods: Forty-five Wistar male rats were used in the study. The rats were divided into 3 groups, each containing eight animals. In the first group, only serum physiologic injections were performed to the temporomandibular joints and identified as the control group. In the second group, arthritis model was created by injecting MAI to the temporomandibular joint. Third group was the study group intraarticular platelet rich plasma injections were performed 4 weeks after monosodium iodoacetate injections.

Results: When cartilage thicknesses were evaluated, there was a significant decrease in group 3 arthritis when compared with other groups. In the study group, cartilage thickness was not significantly different from control groups, but statistically significant improvement was observed when compared to monosodium idoacetate group. Although subchondral cyst formations were also observed in the study group a statistically significant difference was observed between the arthritis group.

Conclusion: We believe that our study results support, and enlightens therapeutic effects of platelet rich plasma on temporomandibular joint arthritis.

Öz

Amaç: Osteoartrit biyomekanik, biyokimyasal, enflamatuvar ve immünolojik reaksiyonların etkisiyle, artiküler kartilajda fokal ve progresif yıkım ile başlayan, subkondral kemikte ve eklem yapılarının tamamında patolojik değişikliklere neden olabilen bir hastalık olarak tanımlanmaktadır. Trombositten zengin plazmanın yapılan klinik çalışmalarda yara ve kemik iyileşmesini hızlandırdığı; şişliği, ağrıyı, enfeksiyonu ve skarı azalttığı; kanama kontrolü sağladığı iddia edilmektedir. Biz

bu çalışmada monosodyum iyodoasetat (MAI) enjeksiyonu ile oluşturulmuş temporomandibüler osteoartrit modelinde intrartiküler trombositten zengin plazma kullanımının etkisini araştırdık.
Gereç ve Yöntemler: Çalışmada 45 adet Wistar tipi erkek sıçan kullanıldı. Sıçanlar her biri sekizer hayvan içerecek şekilde 3 gruba ayrıldı. 1. grupta temporomandibüler ekleme sadece serum fizyolojik enjeksiyonu yapıldı ve kontrol grubu olarak belirlendi. 2. grupta temporomandibüler ekleme MAI enjeksiyonu yapılarak artrit modeli oluşturuldu. Üç grup deney çalışma grubu olarak belirlendi ve monosodyum iyodoasetat enjeksiyonundan 4 hafta sonra intraartiküler trombositten zengin plazma enjeksiyonları yapıldı.
Bulgular: Kıkırdak kalınlıkları değerlendirildiğinde 3. grup artrit grubunda diğer tüm gruplara göre anlamlı derecede azalma mevcuttu. Çalışma grubunda ise kıkırdak kalınlığında kontrol grupları ile anlamlı bir fark bulunmazken, monosodyum iyodoacetat grubuna göre istatistiksel olarak anlamlı iyileşme izlendi. Yine kist oluşumları çalışma grubunda da izlenmesine rağmen, artrit grubu ile arasında istatistiksel olarak anlamlı fark izlendi.
Sonuç: Çalışmamızın trombositten zengin plazmanın temporomandibüler eklem artriti üzerindeki iyileştirici etkileri üzerinde aydınlatıcı ve klinik kullanımı destekleyici olabileceğini düşünüyoruz.

Introduction

Osteoarthritis (OA) is a disease defined with focal and progressive destruction in articular cartilage with the effects of multifactorial reactions and can cause pathologic subchondral bone involvement and joint structures (1). Female patients are commonly affected from temporomandibular joint (TMJ) OA and TMJ dysfunction. Chronic pain, synovitis, cartilage degradation and bone remodeling occurs in pathologic process of OA (2). One major difference of condylar cartilage in the TMJ from other synovial joints is the presence of fibrocartilage containing thick, multi-layered collagen. The degenerative changes of cartilage affect the ability to change physical properties and to resist compression and shear stress. Increased friction between articulating surfaces can cause joint movements to deteriorate and lead to pathological responses to adjacent tissues such as cartilage, capsule, ligaments, synovial membranes, subchondral bone and muscles (3,4).

Many surgical and non-surgical modalities have been proposed and used in the literature, yet no universally accepted treatment exists. TMJ OA continues to be a serious and wide health problem causing significant morbidity (5).

To evaluate TMJ OA pathogenesis and potential treatment strategies an animal model is essential. Mechanical, surgical, spontaneous occurring and drug induced models have been reported in the literature. Knee joint OA model have been successfully induced with intra-articular injection of monosodium iodoacetate (MIA) and widely accepted in literature. There is some recent literature on the use of MIA for creation of both rabbit and rat TMJ OA (6,7).

Platelet-rich plasma (PRP) is a solution formed by centrifugation and condensation of blood, containing high concentrations of platelets. The amount of platelet obtained is 3-8 times that of normal plasma. A large number of mediators are released from the α-granules of these platelets by the addition of thrombin or other activators. PRP contains growth factors such as vascular endothelial growth factor (VEGF), platelet derived growth factor (PDGF), transforming growth factor α and β (TGF α and β), epidermal growth factor (EGF), fibroblast growth factor (FGF), insulin like growth factor (IGF). Almost all these mediators are involved in wound and bone healing and are also effective on angiogenesis. Clinical trials showed that it accelerates the bone and wound healing, decreases swelling, pain, infection and scar formation, and helps hemostasis (8,9).

Because autologous derivation and relatively safe application this product has been used clinically without adequate experimental study. It promises a lot theoretically but still has suspicions due to lack of enough controlled studies. In this study, we investigated the effect of intraarticular injection of PRP in the TMJ OA model induced by MIA injection.

Materials and Methods

This experiment was carried out in the animal laboratory of Adnan Menderes University Faculty of Medicine and approved by Adnan Menderes University Faculty of Medicine Animal Ethics Committee (no: 64583101-2015-113). All experimental procedures were carried out in accordance with the Laboratory Animal Care and Use Health Guide National Institutes. In the study, 35 Wistar male rats (300 and 350 grams) were used. All rats were housed with a 12–12 h light–dark cycle (artificial lighting) with an ambient

temperature of 22±20 °C. Animal feeding needs were regularly met by standard laboratory food and water. All rats were anaesthetized by intramuscular injection with a mixture of %10 ketamin hydrochloride (HCl) (50 mg/kg- Alfamine®-IM) and Xylazin HCl (2,5 mg/kg- Rompun®-IM) during all experimental procedures done by the same surgeon. The experiment was performed after 1-month adaptation period. The rats were divided into 3 groups, each containing eight animals. No injections were made in left sides of the animals. Only intraarticular SF injections were performed in group 1. In group 2, intraarticular MIA injections were performed to create arthritis model. Third group was determined as the study group and intra-articular PRP injections were performed at 4th week after MIA injection.

Preparation of the Platelet-Rich Plasma Solution

Blood required to separate platelets from other blood components and plasma to produce PRP was obtained by intra-cardiac cannulation of 11 selected donor rats under anesthesia with a mixture of ketamine HCl (Alfamine®-IM) and xylazine HCl (Rompun®-IM).

100 mL of blood was collected in four tubes for centrifugation by mixing with citrate-phosphate-dextrose (CPD) solution at 5 mL blood/1 mL CPD ratio to prevent clotting. The CPD solution used was obtained from triple blood bags (Baxter Healthcare Corp, USA) in blood centers. Pooled blood was subjected to centrifugation for 20 minutes at a temperature of 220 °C and a 200 g cycle centrifuge (Heraeus Cryofuge 6000i, Kendo Laboratory Products). A thin intermediate layer (buffy coat) was observed between the light-yellow plasma collected at the top and the red layer at the bottom. This intermediate layer together with the plasma on it was transferred to a separate tube. The tube was centrifuged for 20 minutes at 480 rpm for a second time. The resulting platelet concentrate and platelet poor plasma (= fibrin glue = FG) were separated and taken into different tubes. The platelet concentrate was diluted with FG to 1.5×10 12 platelets/L. Since platelet-rich plasma contained leucocytes in it and was not able to use autologous products in each animal in the study, lymphocyte inactivation was achieved by irradiation with 25 Gy to reduce the "graft versus host" reaction. Platelet rich plasma was activated with bovine thrombin preparation (Thrombin, Sigma-Aldrich, Germany). Thousand units of powdered thrombin containing product was mixed with 10 ml of 10% calcium chloride to obtain thrombin solution at a rate of 100 units/mL. Ten-unit thrombin solution was added to 1 mL of PRP. So that PRP activation and release of growth factors were achieved.

Preparation of Arthritis Model

In 2nd and 3th groups, MIA solution was injected to the TMJs upper compartment to induce TMJ OA. To confirm injection site firstly dye injection of 50 mL was performed to the upper compartment. Than 0.5 mg MIA injection was performed to the right upper compartment TMJs. Left TMJs were left as controls.

Study group was formed by injection into the right TMJs. After 4 weeks, the PRP solution prepared as described above was applied to the MIA injected group. Twelve weeks after the first injection, all rats were sacrificed, exploration was performed, and specimens were taken for histopathological examination. TMJ tissues were completely removed with the surrounding tissues. Samples were taken from the anterior, posterior and lateral sides of the joints and each sample was left in 10% formalin for 24 hours. 5 mm of thick sections were taken from each sample and stained with hematoxylin and eosin (H&E), Masson trichom. Inflammatory changes are classified as 0=no inflammation; 1=mild inflammation (mild congestion and oedema); 2=moderate inflammation (congestion and oedema, small amount of neutrophil leukocytes); 3=severe inflammation (numerous neutrophils and macrophages). Inflammation, subchondral cyst formation and cartilage thicknesses were examined by the same pathologist under microscope (x100 magnification). Statistical comparison of all these data was performed.

Statistical Analysis

Statistical analyses were performed with SPSS (SPSS Inc, USA v 16.0). The mean ± was show standard error of mean, and Mann-Whitney U test and Pearson chi-square were used to compare the groups. $P<0.05$ was statistically significant.

Results

Groups were evaluated for cartilage thickness, inflammation and subchondral cyst formation (Figure 1). When the cartilage thickness was evaluated, there was a significant decrease in the second group

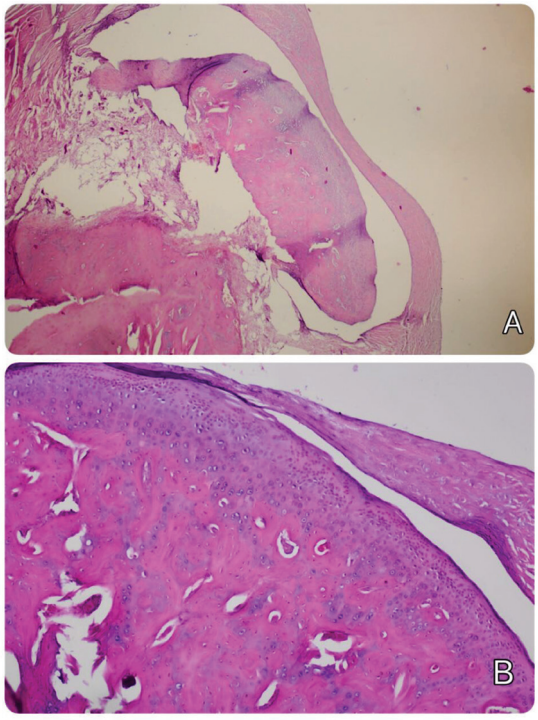


Figure 1. A) Normal temporomandibular joint, cartilage and joint, x20, hematoxylin and eosin. B) Normal joint architecture x100, hematoxylin and eosin

compared to other groups. In the study group, there was no statistically significant difference in cartilage thickness compared to the control group, but a statistically significant improvement exists when compared to the MIA group. Cartilage thickness was found to be significantly decreased in the arthritis group compared to the other groups and no significant difference was found between the other groups (Figure 2) (Graphic 1).

İnflammation was found to be significantly increased in the MIA group. Also, an increased number of subchondral cyst formations were observed in the MIA group compared to other groups. Although cyst formations were also observed in the study group, there was a statistically significant difference with the arthritis group (Figure 2) (Tables 1, 2).

Discussion

TMJ diseases are very common spectrum disorders and OA is reported as an important subtype. In the pathogenesis of this disease, there are changes in the subchondral bone and joint structures, beginning with focal and progressive destruction in the articular

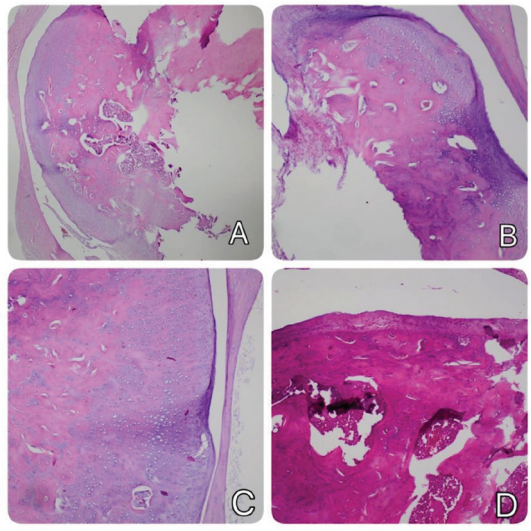
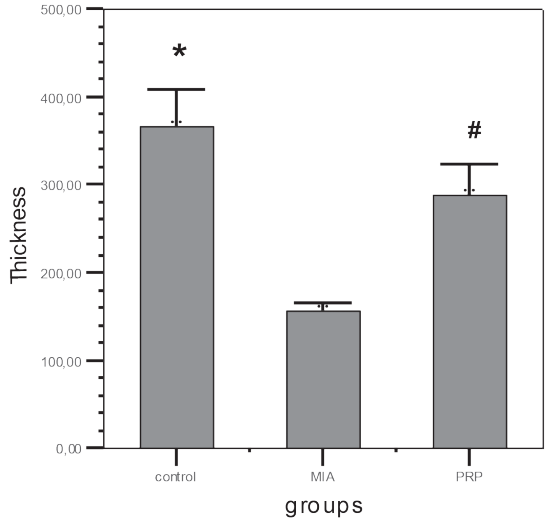


Figure 2. A) Increased trabecular bone, x40, hematoxylin and eosin. B) Subchondral cyst formations in monoamine iodoacetate group, x100, hematoxylin and eosin. C) Increased cartilage thickness in platelet-rich plasma group, x200, hematoxylin and eosin. D) Thin and deformed cartilage and increased trabeculation in monoamine iodoacetate group, x100, hematoxylin and eosin



Graphic 1. Temporomandibular cartilage thicknesses of the groups
*p<0.05 control vs MIA, #p<0.05 control vs PRP
MIA: Monoamine iodoacetate, PRP: Platelet-rich plasma

cartilage with the effects of the inflammatory and immunological reactions (10).

Until now, TMJ OA animal models have been tried to be formed by various methods including surgical, mechanical, drug-induced and spontaneously occurring methods. Surgically induced and

Table 1. Subchondral cyst formation in groups

	Groups			
	Control	MIA	PRP	Total
Subchondral cysts* (-)	7	0	5	12
Subchondral cysts (+)	1	8	3	12
Total	8	8	8	24

Subchondral cysts groups Crosstabulation: *p<0.05 compared three groups. MIA: Monoamine iodoacetate, PRP: Platelet-rich plasma

Table 2. İnflammation in groups

Inflammation grade*	Groups			
	Control	MIA	PRP	Total
0	6	0	0	6
1	2	0	5	7
2	0	3	3	6
3	0	5	0	5
Total	8	8	8	24

Inflammation groups Crosstabulation: *p<0.05 compared three groups. MIA: Monoamine iodoacetate, PRP: Platelet-rich plasma

spontaneous methods are limited due to slow progression and complicated operative nature of TMJ. Therefore, studies focusing drug-induced models to be cartilage damage models instead of OA models. A simple and reproducible animal model of TMJ OA that mimics clinically and histopathologically is still necessary (11).

MIA injections are widely used in the literature to induce OA-like lesions in knee joints.

MIA mainly inhibits glyceraldehyde-3-phosphate dehydrogenase activity and leads to apoptosis of chondrocytes. With the modification of the MIA concentration, the progression of articular lesions and the severity of lesions can be easily modulated. In experimental researches and drug toxicology tests rats are the primal test animals.

It has been shown that MIA injection to rat TMJ causes OA like lesions. Considering all above we selected the arthritis model induced by MIA injection in the rat TME joint. A simple and reliable rat model of TMJ OA have been described by Wang et al. (12) by intra- articular MIA injections.

Due to risk of serious complications, difficulty of surgical field, uncertainty of outcomes and low surgery motivation of patients, surgical treatment options are indicated and possible only in certain select group of TMJ OA patients. Intraarticular corticosteroid injection is widely used in OA treatment. Although single intraarticular injections have successful results in relieving symptoms, complications such as cartilage damage, bone necrosis, soft tissue atrophy lead to progression of existing joint disease in repeated injections. It is suggested that intraarticular corticosteroid injection reduces inflammation in rat TMJ but increases osteoclastic activity in the condyle and intraarticular injection of this substance may increase bone resorption risk. Harmful side effects of corticosteroids have also prompted the search for new therapeutic agents (13). Duygu et al. (14) demonstrated that intra-articular injection of hyaluronic acid (HA) decreased the cartilage changes in early stage OA in rabbit TMJ but there is no clinical consensus over HA usage and effects so far.

PRP also termed autologous platelet gel is essentially an increased concentration of autologous platelets suspended in a small amount of plasma after centrifugation at 2 different frequencies. PRP is a natural source of growth factors such as PDGF, IGF, VEGF, EGF, FGF and TGF-β (15).

The amount of platelet obtained is 3-8 times that of normal plasma. A large number of mediators are released from the α-granules of the platelets by the addition of thrombin to this product. Almost all of these are mediators that are involved in wound and bone healing and are also effective on angiogenesis. Clinical trials showed that it accelerates the bone and wound healing, decreases the swelling, pain, infection and scar formation, and helps the hemostasis (16). Hancı et al. (17) showed the effect of PRP on TMJ disorders and compared with arthrocentesis. Hegab et al. (18) demonstrated the effect of PRP on OA and compared with HA injections. Although these clinical studies are valuable, assessment of effects is subjective as it depends on patient surveys.

Because of autologous production, this product has been used clinically without adequate experimental study. It promises a lot theoretically but still has suspicions due to absence of adequate controlled studies. In this study, we investigated the effect of intraarticular PRP in the TMJ OA model induced by MIA injection and interpreted the results histologically which is not present and possible in clinical studies.

Increased degenerative changes, increased subchondral cyst formation and decrease in cartilage

thickness were detected in the MIA induced arthritis group when compared with other groups. This finding indicates that MIA injection to the upper compartment of TMJ successfully formed an arthritis model consistent with the literature.

Increased cartilage thickness and decreased subchondral cyst formation and degenerative changes in the study group compared to the arthritis model demonstrate the protective effect of PRP administration on the degenerative effects of arthritis. A significant decrease in cartilage changes was found in control and study group and MIA group between at 12th weeks ($p<0.05$). Cartilage damage and cartilage matrix degradation is prevented by the anti-inflammatory effects of PRP.

Inflammation was statistically increased in the MAI group and in study group there were no statistically meaningful difference between the control groups which suggests the anti-inflammatory protective activity of PRP. Subchondral cyst formation even exists in PRP group there were statistically meaningful increase in MIA group. These findings all together points beneficial role of PRP derived cytokines and growth hormones in repair of OA in the joint.

Failure to perform repetitive PRP injection, lack of electron microscopic and micro CT scanning examinations are the weaknesses of this study but we think that PRP application, which is still used in other joint arthritis treatment, has a place in treatment of TMJ OA especially in patients who are not suitable for advanced surgery.

Conclusion

Further randomized clinical and experimental studies are needed to clarify the effects of PRP administration and we also believe that stem cell and PRF applications may be informative and supportive on clinical use of the role of PRP.

Ethics

Ethics Committee Approval: This study was approved by the Adnan Menderes University Faculty of Medicine Animal Ethics Committee (no: 64583101-2015-113).

Informed Consent: All experimental procedures were carried out in accordance with the Laboratory Animal Care and Use Health Guide National Institutes.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: H.S.Ö., S.İ., H.K., T.D.Y., K.Ç., Concept: H.S.Ö., S.İ., Design: H.S.Ö., S.İ., Data Collection or Processing: H.S.Ö., S.İ., Analysis or Interpretation: H.S.Ö., S.İ., C.T., Literature Search: H.S.Ö., S.İ., Writing: H.S.Ö., S.İ., H.K., T.D.Y., K.Ç.

Conflict of Interest: No conflict of interest was declared by the authors.

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Original Article / Özgün Araştırma

A Marker for Evaluation of Oxidative Stress in Patients with Alopecia Areta: Thiol-Disulphide Homeostasis

Alopesi Areata Tanılı Hastalarda Oksidatif Stresin Değerlendirilmesinde Bir Belirteç: Tiyol-Disülfid Homeostazı

Suzan Demir Pektaş[1], Emine Tuğba Alataş[1], Gürsoy Doğan[1], Salim Neşelioğlu[2], Özcan Erel[2]

[1]Muğla Sıtkı Koçman University Faculty of Medicine, Department of Dermatology, Muğla, Turkey
[2]Yıldırım Beyazıt University Faculty of Medicine, Department of Biochemistry, Ankara, Turkey

Abstract

Objective: Alopecia areata (AA) is a disorder characterized by non-scarring hair loss, whose etiology involves oxidative stress. We aimed to determine the role of thiol/disulphide levels in AA pathogenesis and to investigate if they can be used as its marker.

Materials and Methods: This prospective study included 100 AA patients who presented to dermatology outpatient clinic and 100 healthy controls without any systemic and/or inflammatory dermatological disorder. The control and study groups were compared with respect to native thiol, total thiol, and disulphide levels, and disulphide/native thiol, disulphide/total thiol, and native thiol/total thiol ratios. The relationships between demographic and lesion characteristics, native thiol, total thiol, and disulphide levels, and disulphide/native thiol, disulphide/total thiol, and native thiol/total thiol ratios were studied.

Results: The mean age of AA patients was 37.5 years. Fifty-eight (58%) patients were male, and the median body mass index was 24 kg/m^2. Median age was significantly higher in the AA group ($p<0.05$). The AA group had a significantly lower total and native thiol level, native thiol/total thiol ratio, significantly higher disulphide level, disulphide/native thiol ratio, and disulphide/total thiol ratio ($p<0.05$ for all comparisons). There was no correlation between the parameters of thiol/disulfide hemostasis and demographic and lesion characteristics ($p>0.05$).

Conclusion: The thiol/disulphide homeostasis shifted towards oxidative stress, and a decrease in thiols and an increase in disulphides were found in the AA patients. This finding may be responsible for diffuse destruction of hair follicle in the pathogenesis of AA.

Keywords
Alopecia areata, oxidative stress, thiol-disulphide homeostasis

Anahtar Kelimeler
Alopesi areata, oksidatif stres, tiyol/disülfid hemostazı

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Address for Correspondence/Yazışma Adresi:
Suzan Demir Pektas MD,
Muğla Sıtkı Koçman University Faculty of Medicine, Department of Dermatology, Muğla, Turkey
Phone : +90 506 810 02 22
E-mail : suzandpektas@gmail.com
ORCID ID: orcid.org/0000-0001-5074-986X

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Öz

Amaç: Alopesi areata (AA) etiyolojisinde oksidatif stresin rol aldığı, skarsız kıl kaybı ile karakterize bir hastalıktır. AA hastalarında tiyol/disülfid düzeylerine bakarak AA patogenezindeki rolünü ve AA patogenezinde bir belirteç göstergesi olup olmayacağının araştırılması amaçlanmıştır.

Gereç ve Yöntemler: Bu kesitsel çalışma 27.07.2016-01.02.2017 tarihleri arasında dermatoloji polikliniğine başvuran AA tanısı alan 100 hasta ve herhangi bir sistemik ve/veya enflamatuvar deri hastalığı olmayan 100 gönüllü kontrol grubunda

gerçekleştirildi. Kontrol ve hasta grubu arasında nativ tiyol, total tiyol, disülfid düzeyi, disülfid/nativ tiyol, disülfid/total tiyol ve nativ tiyol/total tiyol oranları karşılaştırıldı. AA hastalarının demografik ve lezyon özellikleri ile nativ tiyol, total tiyol, disülfid düzeyi, disülfid/nativ tiyol, disülfid/total tiyol ve nativ tiyol/total tiyol oranları arasındaki ilişki incelendi.

Bulgular: AA'lı hastaların yaş ortalaması 34,9±10,4 yıl, %58'i erkek ve vücut kitle indeksi ortancası 24 kg/m^2 olup, kontrol grubu ile yaş ortalaması açısından farklılık saptanmadı (p>0,05). AA hastalarında total tiyol düzeyi, nativ tiyol düzeyi ve nativ tiyol/total tiyol oranında düzeylerinde anlamlı düşüklük saptanırken; disülfid düzeyi, disülfid/nativetiyol ve disülfid/total tiyol oranlarında anlamlı yükseklik saptandı (p<0,05). AA hastalarında lezyonun süresinin, lezyon paterninin, lezyonun genişliğinin ve rekürrens sıklığının; total tiyol, nativ tiyol, disülfid düzeyleri, disülfid/nativ tiyol, disülfid/total tiyol, nativ tiyol/total tiyol oranlarıyla arasında istatistiksel olarak anlamlı bir ilişkiye rastlanmadı (p>0,05).

Sonuç: AA hastalarında mevcut mekanizmalardan biri oksidatif stres artışıdır. AA grubunda tiyol/disülfid hemostazı oksidatif stres lehine bozulmuş olup, bu hastalarda tiyollerde azalma, disülfid miktarında artma belirlenmiştir.

Introduction

Alopecia areata (AA) is a disease characterized by non-scarring hair loss, which constitutes for 0.7-3.8% of all dermatoses (1,2). Although its prevalence varies between countries, it is estimated to be between 1.7% and 2% (3,4). Whereas its etiology and pathogenesis are not entirely clear, it has been reported that many factors such as autoimmunity, genetic tendency, family history, environmental factors, infectious agents, drugs, trauma, infection, oxidative stress, and psychological stress are responsible at various degrees.

The antioxidant properties of sulphur containing amino acids are variable (5). Thiols are both antioxidant and pro-oxidant molecules. The level of oxidative stress in an organism determines thiols' antioxidant and pro-oxidant effects. This balance has a dynamic status and reflects the overall condition of an organism (6,7).

Plasma thiols are organic compounds that contain sulfhydryl groups composed of hydrogen, sulphur, and carbon atoms. They are strong antioxidants that physiologically eliminate free radicals (8). Reactive oxygen species (ROS) forming in an organism cause oxidation and form disulphide bonds by transferring excess electrons to thiols. Those bonds are reversible and, depending on the oxidant-antioxidant balance, electrons may return back to thiols (6,9,10). The antioxidant effect of thiol-disulphide homeostasis has a critical role in signal transduction, enzymatic reactions, transcription, detoxification, apoptosis reaction, regulation of enzymatic activation, and cellular signal mechanisms. Under normal circumstances the thiol-disulphide homeostasis has a dynamic pattern and is affected by disease states resulting from oxidative stress (6,9). According to a widely accepted view, the changes in thiol-disulphide homeostasis would provide important clues about various abnormal biochemical processes in pathological conditions causing oxidative stress (6). In the present study we aimed to investigate the role of thiol-disulphide homeostasis in AA pathogenesis and to find out if it can be used as its marker.

Materials and Methods

This prospective case-control study was conducted by the Department of Dermatology at Muğla Sıtkı Koçman University Training and Research Hospital (Muğla, Turkey) and Department of Biochemistry at Ankara Yıldırım Beyazıt University Training and Research Hospital (Ankara, Turkey) between 27.07.2016-01.02.2017. Ethical approval (date: 27.07.2016, no: 13/III) was obtained from Muğla Sıtkı Koçman University Local Ethics Committee and written informed consent was obtained from all patients and controls before the start of the study. It involved 100 patients with AA who presented to the dermatology outpatient clinic and 100 healthy volunteers who free of any systemic or skin disorder. Our study was performed in accordance with the guidelines of good clinical practice and the Helsinki declaration.

Persons with any systemic disorder (coronary artery disease, liver failure, renal failure, malignancy etc.), inflammatory skin disorders, smoking/alcohol consumption, and systemic/topical drug use were excluded, as were those who were pregnant, breastfeeding, and younger than 18 years of age. Age, sex, AA duration, lesion size, and recurrence status were recorded in all cases. Native thiol, total thiol, disulphide levels and disulphide/native thiol, disulphide/total thiol, and native thiol/total thiol ratios were compared between the patient and control group's sera. The correlations between AA lesion

properties and total thiol, native thiol, and disulphide levels as well as disulphide/native thiol, disulphide/total thiol, and native thiol/total thiol ratios were studied. The samples were centrifuged at 3600 rpm for 10 minutes at the biochemistry laboratory and kept at -80 degrees celsius until the final biochemical analysis. All samples were thawed simultaneously, and serum thiol-disulphide parameters were studied at Yıldırım Beyazıt University, Ankara Training and Research Hospital Biochemistry Laboratory, with a Roche Hitachi Cobas c501 automatic analyzer and using the automatic measurement method recently developed by Erel and Neselioglu (6).

Statistical Analysis

SPSS for Windows 18.0 software package was used for statistical analyses. The Kolmogorov-Smirnov test was used to test the normality of the distribution of continuous variables. The descriptive statistics included mean and standard deviation for normally distributed quantitative variables and median and interquartile range (IQR) for non-normally distributed quantitative variables. Categoric variables were presented as number and percentage (%). Variables with non-normal distribution were compared using the Mann-Whitney U test, and categoric variables were compared using the Pearson's chi-square test. Pearson correlation test was used for comparison of normally distributed quantitative variables. A p value of less than 0.05 was considered statistically significant.

Results

The median age of AA patients was 37.5 (IQR: 11) years, and 58 (58%) of them were male. The median body mass index (BMI) was 24 kg/m^2. The mean age was significantly higher in the AA group ($p<0.05$). No statistically significant difference was found between the groups with respect to gender and BMI ($p>0.05$) (Table 1).

The AA group had a significantly decreased native thiol level ($p<0.05$) (Table 2). The AA group had a significantly decreased native thiol/total thiol ratio and a significantly increased disulphide level, disulphide/native thiol, and disulphide/total thiol ratios ($p<0.01$) (Table 2). The total thiol level was similar between the AA and control groups ($p>0.05$) (Table 2).

Demographic properties of the patients are shown on Table 1. No correlation was found between the

Table 1. Comparison of demographic and clinical characteristics of the study groups

		AA patients	Control	p
Age, mean ± SD		37.5 (11)	32 (16)	0.002
Gender	Male, n (%)	58 (58)	47 (47)	0.119
	Female, n (%)	42 (42)	53 (53)	
BMI, median (IQR)		24 (0)	24 (1)	0.214
Disease duration	6 months >, n (%)	28 (28)	-	-
	6 months <, n (%)	72 (72)	-	-
Disease pattern	Mono AA, n (%)	42 (42)	-	-
	Poli AA, n (%)	55 (55)	-	-
	AA Totalis, n (%)	3 (3)	-	-
Lesion size	S1 (<%25), n (%)	69 (69)	-	-
	S2 (%25-49), n (%)	26 (26)	-	-
	S3 (%50-74), n (%)	2 (2)	-	-
	S4 (%75-90), n (%)	2 (2)	-	-
	S5 (%100), n (%)	1 (1)	-	-
Disease recurrence	First, n (%)	68 (68)	-	-
	1. Recurrence, n (%)	24 (24)	-	-
	2. Recurrence, n (%)	5 (5)	-	-
	3. Recurrence, n (%)	3 (3)	-	-

AA: Alopecia areata, SD: Standard deviation, IQR: Interquartile range

Table 2. Comparison of thiol-disulphide homeostasis parameters of the study groups

	AA patients (n=100) median (IQR)	Controls (n=100) median (IQR)	p
Native thiol	404.1 (94.2)	424.7 (87.9)	0.006
Total thiol	441 (103.4)	456.5 (90.8)	0.071
Disulphide	20.7 (8.1)	15.65 (7.2)	<0.001
Disulphide/native thiol	5.3 (2.2)	3.7 (1.7)	<0.001
Disulphide/total thiol	4.8 (2.1)	3.4 (1.4)	<0.001
Native thiol/total thiol	90.3 (4.3)	93.1 (2.9)	<0.001

AA: Alopecia areata, IQR: Interquartile range

total thiol level, native thiol level, and native thiol/total thiol ratio and significantly increased disulphide level, disulphide/native thiol, and disulphide/total thiol ratios levels as analyzed by BMI, lesion duration, disease pattern, and recurrence frequency (p>0.05) (Table 3).

Discussion

AA is an autoimmune disorder characterized by the destruction of hair follicles by T cells (2,3). AA generally starts at a young age and it adversely affects quality of life by its psychological burden (11,12). It is of debate whether oxidative stress develops primarily or as a result of T cell infiltration (13). It has been shown that oxidative stress is augmented, and oxidative balance is impaired in disorders with inflammatory or autoimmune reactions, such as AA, atopic dermatitis, pemphigus, psoriasis, allergic contact dermatitis, acne vulgaris, and vitiligo (2,14-16). Although AA has a well-known close association with autoimmunity, the role of oxidative stress in its pathophysiology has not been clearly demonstrated (2,13,17,18). It has been reported that lipid peroxidation may play a role in AA pathogenesis and may increase total oxidant capacity/total antioxidant capacity (5,19). ROS is activated by abnormal lymphokine release, eicosanoid metabolism, fatty acid metabolism, and inflammatory cells surrounding the hair follicle (20).

We detected significant decreases in total thiol level, native thiol level, and native thiol/total thiol ratio, but significant increases in disulphide level, disulphide/native thiol ratio, and disulphide/total thiol ratio in the AA patients.

Kilinc et al. (21) reported that the disulfide/native thiol and native thiol/total thiol ratios and native thiol, total thiol, and disulfide values were similar in AA patients and the control group. Akbas et al. (8) reported that disulphide/thiol ratio increased in chronic urticaria and increased oxidative stress reduced disulphide ratio in chronic stage.

Our study suggested that thiols are reduced in AA as a result of increased oxidative stress. An important step in hair formation is the thiol-disulphide conversion that occurs simultaneously with the process of hair formation (22). It is thought that thiol transfer is the basic mechanism underlying the non-enzymatic thiol-disulphide conversion (23). In the enzymatic reaction, on the other hand, it has been shown that the enzyme catalyzing thiol-disulphide conversion of cystine and glutathion or other low molecular weight compounds is actually a two-substrate mechanism involving thiol transfer (23). Histochemical examination of hair has shown that in the trichilemmal sac encircling hair the germinal cells rich in free thiol groups are abundant, and disulphide bonds limit themselves (24). In cases of failed hair formation or absent hair follicle, on the other hand, thiol ratio decreases and sulphide content increases (22). Previous studies have indicated increased oxidative activity and decreased antioxidant activity in the scalps of AA patients (13,14,18,25). Free radicals originating from normal metabolism or pathological processes and increased oxidative stress break off one proton from various molecules including thiols and fatty acids and form new radicals, ultimately leading to cellular injury (8,26,27). Degradation of thiol balance may explain cellular damage (28). In our study, we believe that in AA thiols are consumed as a consequence of increased oxidative stress, leading to the conversion of this thiol-disulfide into AA pathophysiology.

Table 3. Correlations of thiol/disulphide hemostasis parameters with demographic and clinical characteristics of the study patients

	BMI		Disease duration		Lesion size		Lesion pattern		Recurrence	
	r	p	r	p	r	p	r	p	r	p
Native thiol	0.023	0.819	0.005	0.957	0.037	0.712	0.084	0.408	-0.117	0.248
Total thiol	0.021	0.832	-0.010	0.925	0.028	0.783	0.067	0.509	-0.121	0.232
Disulphide	-0.019	0.853	0.115	0.256	0.056	0.582	0.025	0.803	-0.070	0.491
Disulphide/native thiol	-0.027	0.791	-0.088	0.385	-0.100	0.324	-0.157	0.118	0.046	0.651
Disulphide/total thiol	-0.028	0.785	-0.099	0.328	-0.103	0.308	-0.171	0.088	0.057	0.571
Native thiol/total thiol	0.023	0.821	-0.120	0.233	0.084	0.405	0.153	0.127	0.039	0.701

BMI: Body mass index

It has been previously reported that while total thiol levels are correlated to oxidative stress and disulphide levels in oxidative stress, native thiol ratio is not necessarily correlated to disulphide levels (8,29). This can be attributed to a greater decrease in total thiol than native thiol in oxidative stress. Hence, our study showed a reduced disulphide/total-native thiol ratio but an increased native/total thiol ratio, which can be attributed to a lesser consumption of native thiol in AA.

Kilinc et al. (21) reported that thiol/disulfide values were not associated with gender, disease duration, number of lesions, or recurrence frequency in AA patients. Akar et al. (18) reported that oxidation was augmented in the acute stage compared to the chronic stage. Akbas et al. (8) showed that thiol/disulfides did not change in cases of acute urticaria but decreased in chronic cases, and there was a significant relationship between disease severity and thiol/disulfide level. Abdel Fattah et al. (13) reported a positive correlation between lesion size and oxidative stress factors. Heidarloo and Adışen (2) found no correlation between oxidant levels and AA lesion severity, and they attributed it to the majority of cases being S1. In our study, there no correlation observed between total thiol level, native thiol level, and native thiol/total thiol ratio and significantly increased disulphide level, disulphide/native thiol and disulphide/total thiol ratios levels as analyzed by BMI, lesion duration, disease pattern, and recurrence frequency. There was a shift of thiol-disulphide homeostasis towards oxidation, albeit statistically non-significant, in patients with a disease duration of less than 6 months, which may suggest that oxidation is more prominent in the acute stage of the disease. We believe the thiol-disulphide homeostasis had higher levels in patients with larger lesions and wider pattern but the low number of patients in this group possibly prevented the occurrence of statistical significance. We believe that this is related to disease process starting over each time rather than AA's attack frequency.

Conclusion

In conclusion, it can be suggested that oxidative stress is one of the possible mechanisms playing a role in the pathophysiology of AA. In the AA patients, the thiol/disulphide homeostasis shifted towards oxidative stress, and a decrease in thiols and an increase in disulphides were also observed. This condition may be related to thiol-disulfide conversion of thiol in case of oxidative stress. Large-volume studies are needed in order to fully elucidate these mechanisms.

Ethics

Ethics Committee Approval: Ethical approval (date: 27.07.2016, no: 13/III) was obtained from Muğla Sıtkı Koçman University Local Ethics Committee before the start of the study.

Informed Consent: The written informed consent was obtained from all patients and controls before the study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: S.D.P., E.T.A., Concept: S.D.P., G.D., E.T.A., Design: S.D.P., E.T.A., G.D., Data Collection or Processing: S.D.P., G.D., E.T.A., Analysis or Interpretation: S.D.P., S.N., Ö.E., Literature Search: S.D.P., Writing: S.D.P.

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Original Article / Özgün Araştırma

Effects of Robotic Rehabilitation on Motor Functions in Children with Cerebral Palsy

Serebral Palsili Çocuklarda Robotik Rehabilitasyonun Motor Fonksiyon Üzerine Etkileri

Meral Bilgilisoy Filiz[1], Naciye Füsun Toraman[1], Can Mehmet Ali Çiftçi[2], Tuncay Çakır[3], Şebnem Koldaş Doğan[1], Hüseyin Arslan[4]

[1]University of Health Sciences, Antalya Training and Research Hospital, Clinic of Physical Medicine and Rehabilitation, Antalya, Turkey
[2]BAMA Technology, Teknokent, Middle East Technical University, Ankara, Turkey
[3]Private Likya Hospital, Clinic of Physical Medicine and Rehabilitation, Antalya, Turkey
[4]Sandıklı State Hospital, Clinic of Physical Medicine and Rehabilitation, Afyon, Turkey

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Anahtar Kelimeler
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Address for Correspondence/Yazışma Adresi:
Meral Bilgilisoy Filiz MD,
University of Health Sciences, Antalya Training and Research Hospital, Clinic of Physical Medicine and Rehabilitation, Antalya, Turkey
Phone : +90 505 647 58 40
E-mail : mbilgilisoy@gmail.com
ORCID ID: orcid.org/0000-0002-3064-2878

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Abstract

Objective: The aim of this study was to investigate the effects of robotic rehabilitation (RR) on spasticity and motor functions of children with varying types and functional levels of cerebral palsy (CP).

Materials and Methods: A total of 28 children were evaluated aged 6-16 years, with level 2-4 CP according to the Gross Motor Function Classification System (GMFCS) who were planned to undergo 30 sessions of RR. Motor functions were evaluated before and after RR using the Gross Motor Function scale-66 (GMFS-66) B, C, D and E dimensions, gastrosoleus spasticity with the Modified Ashworth scale (MAS) and a target was defined for each patient with a Goal Attainment scale (GAS). Following the RR treatment, the efficacy was evaluated by grouping the patients according to the GMFCS level and the type of CP.

Results: 11% of the patients were at level 2, 36% were at level 3, and 54% were at level 4.61% of them were identified as bilateral spastic, 21% unilateral spastic and 14% mixed type. The patients comprised 50% male and 50% female children with a mean age of 10.8±2.7 years. Mean participation in the RR program was 23±9.6 sessions. A statistically significant improvement was determined in the D dimension of the GMFS in the children at level 2 and 3 of GMFCS ($p<0.05$), and there were no differences in respect of the MAS and GAS ($p>0.05$). No differences were determined between the type of CP groups in respect of GMFS, MAS and GAS.

Conclusion: It was concluded that the application of RR was of benefit for the children with CP at the level 2 and 3 of GMFCS in respect of the development of standing activities.

Öz

Amaç: Bu çalışmanın amacı, farklı fonksiyon düzey ve tipteki serebral palsili (SP) çocuklarda robotik rehabilitasyonun (RR), spastisite ve motor fonksiyonlara etkisini araştırmaktır.

Gereç ve Yöntemler: Otuz seans RR planlanan, 6-16 yaş arasında, Kaba Motor Fonksiyon Sınıflama Sistemi (KMFSS) 2-4 düzeyinde olan 28 SP'li çocuğun sonuçları değerlendirildi. RR öncesi ve sonrasında fonksiyon Kaba Motor Fonksiyon ölçüm-66

(KMFÖ-66) B, C, D, E boyutları ile, gastrosoleus spastisitesi Modifiye Ashwort skalası (MAS) testi ile değerlendirildi ve her hasta için Hedefe Ulaşma skalası (HUS) ile hedef belirlendi. RR tedavisi sonrası, KMFSS düzeyi ve SP tipine göre gruplama yapılarak etkinlik değerlendirildi.
Bulgular: Çocukların %11'i evre 2, %36'sı evre 3, %54'ü evre 4'de, %61'i bilateral spastik, %21'i unilateral spastik, %14'ü miks tipteydi. Hastaların %50'si erkek ve ortalama yaş 10,8±2,7 yıldı. RR programına ortalama katılım 23±9,6 seanstı. RR sonrası KMFSS evre 2 ve 3 çocuklarda KMFÖ, D boyutunda gelişme olduğu saptandı ($p<0,05$), MAS ve HUS yönünden fark yoktu ($p>0,05$). SP tipine göre gruplar arasında KMFÖ, MAS ve HUS yönünden anlamlı fark saptanmadı.
Sonuç: RR uygulamasının, KMFSS 2 ve 3 evredeki çocuklarda ayakta durma aktivitelerinin gelişmesinde yararlı olduğu kararına varıldı.

Introduction

One of the targets in cerebral palsy (CP) rehabilitation is to provide mobility according to the expectations of the patient, the clinical examination findings and patient characteristics. Therefore, in rehabilitation programs there has been increasing widespread use of robotic technology that has been developed with the aim of facilitating or correcting the gait, thereby providing functional walking (1-3). Robot-assisted gait training is based on the principles of sensorimotor learning. Through the intensive and repeated visual and auditory stimuli given in the different phases of walking, it is intended to regain functional ambulation (4).

There is not yet considered to be sufficient information to be able to form recommendations for robot-assisted walking in CP childen (5,6). Some studies have reported that robot-assisted walking has provided an increase in gross motor skills, walking speed and resistance (4,7-13), and an increase in participation and performance of daily living activities (9,14). However, it has been claimed that there is a need for stronger evidence of the role and efficacy of robot-assisted walking in the clinical treatment of CP children (10,15).

There have been seen to be conflicting results related to the efficacy of robot-assisted walking training in CP children at different motor functional levels (7,13,16). van Hedel et al. (7) reported developments in mobility and gross motor function in children of level 3 and 4 according to the Gross Motor Function Classification System (GMFCS), while there was no development in level 2 children. Borggraefe et al. (13) determined a greater development in gross motor function in level 1 and 2 children compared to those of level 3 and 4. In a study by Willoughby et al. (16) it was reported that gait training on a walking band was of more benefit to children who were more severely affected functionally. However, to the best of our knowledge, there has been no previous study that has investigated the efficacy of robotic rehabilitation (RR) in different types of CP. Therefore, the aim of this study was to evaluate the response to RR in terms of motor function development in children with different types and motor functional level of CP, who were planned to undergo robot-assisted walking training.

Materials and Methods

The data of children with CP, aged 6-16 years, who applied to the outpatient clinic of physical therapy (PT) and rehabilitation department and who were eligible for RR were analysed retrospectively. The Ethics Committee of the University of Health Sciences, Antalya Training and Research Hospital approved the study (approvel number: 2015-029). A total of 30 sessions of RR was scheduled for the children with CP who were at GMFCS level 2-4, had received no botulinum toxin injections or surgical treatment within the previous 3 months, had sufficient mental function and did not have treatment-resistant epilepsy, any sight or hearing problem, contracture of the lower extremity, fracture or joint instability, hip dislocation or any circulation problems. Motor functions were evaluated using the Gross Motor Function scale (GMFS), and gastrosoleus spasticity with the Modified Ashworth scale (MAS). Taking the GMFS results into consideration and using a Goal Attainment scale (GAS), a target was defined for each patient. All evaluations were performed twice, before and after RR, in all patients.

The GMFCS is a standardised method that classifies gross motor function in CP Children into 5 levels: level 1, walking without restriction; level 2, walking with restriction; level 3, walking with a hand-held assistive device; level 4, limited independent movement and can use a motorised mobility device; level 5, moved by wheelchair (17).

Classification according to the type of CP was made according to the Surveillance of Cerebral Palsy in Europe (SCPE) and was defined as bilateral spastic, unilateral spastic and mixed (18). Although there is no mixed type in the SCPE classification, the presence of spasticity and ataxia together was defined as mixed type.

To measure the gross motor functions, the standard points of the GMFS were calculated. This scale comprises 66 items in 5 dimensions in terms of A, lying and turning (4 items); B, sitting (15 items); C, crawling-kneeling (10 items); D, standing (13 items); and E, walking, running, jumping (24 items) (19). In the study, lying and turning functions were not evaluated, so dimensions B, C, D and E were calculated for evaluation.

The MAS was applied to classify gastrosoleus spasticity. Resistance to passive motion was measured on the following 5-point scale: 0) no increased resistance; 1) slightly increased reisitance; 2) clear resistance throughout most of the range of motion; 3) strong resistance, movement is difficult; 4) rigit flexion or extension (20).

GAS is an individualized, goal-oriented measurement tool rated by the physician and patient to track functional improvement; scores ranged from –3 (worse than start) to +2 (much more than expected, improvements clearly exceeded the defined therapeutic goal) based on a 6-point scale. Active and/or passive goals were set for each child by the patient and the investigator at screening based on the GMFS results and the performance of the child (21) (Table 1).

The RR application as performed 5 days per week, 40 min per session, 30 sessions in total with the RoboGait (BAMA Technology, Turkey) device, which is a robot-aided gait training system that helps the patients improve their walking abilities. The system was composed of a suspension system which could move the patient up and down, backwards and forwards, a screen providing feedback on the interaction of the patient and formed as a robotic walking orthosis providing active movements of the legs and the low-speed walking band on which the patient is walking. The robotic orthosis has motors providing active movement in the hip and knee joints and power sensors measuring the torque on the joints.

Statistical Analysis

All statistical analyses were applied using SPSS version 18.0 software. The differences in the GMFS, MAS and GAS data before and after treatment were calculated and values recorded as median, minimum and maximum. In the comparison of the gender distribution in the groups, the chi-square test was used, and for intra-group evaluations, the Wilcoxon test. The differences before and after RR were compared between groups using the Kruskal-Wallis test. For the comparison of significant data between groups, the Mann-Whitney U test was applied. A value of $p<0.05$ was accepted as statistically significant.

Results

The study included 28 children with CP; 14 males and 14 females. The GMFCS levels were 2 in 11%, 3 in 36% and 4 in 54%. All the GMFCS level 2 children were unilateral spastic, those at level 3 were 20% unilateral spastic, 70% bilateral spastic and 10% mixed type. Those at level 4 were 7% unilateral spastic, 7% dyskinetic, 67% bilateral spastic and 20% mixed type. The 1 child who was dyskinetic was not included in the statistical evaluation.

The age and duration of each session were smilar in all patients when they were stratified according to the GMFCS or CP type ($p>0.05$). The number of RR sessions in the bilateral spastic group was greater than in the mixed group ($p=0.031$) (Tables 2, 3).

At baseline, there were no differences between the GMFCS groups in respect of GMFS-B and MAS ($p>0.05$). A statistically sinificant difference was determined between the groups in respect of GMFS-C, (chi-square=11.770, $p=0.003$), GMFS-D, (chi-square=15.332, $p<0.001$), and GMFS-E (chi-square=17.138, $p<0.001$). The points of the level 2 children were higher than those of the level 3 and 4 children, and the points of the level 3 children were higher than those of level 4 ($p<0.05$) (Table 2).

At baseline, there were no differences between the CP type groups in respect of GMFS-B, C and E points ($p>0.05$). The GMFS-D points were determined to be different between the groups (chi-square=7.805, $p=0.020$). No difference was determined between the bilateral spastic and the mixed group in respect of the GMFS-D points ($p>0.05$). The GMFS-D (standing) points of the unilateral spastic group were higher than those of the bilateral spastic group ($p<0.05$).

In intra-group comparisons according to the GMFCS level, of before and after treatment, no significant differences were observed in the GMFCS level 2 children in respect of all the GMFS, MAS and GAS (p>0.05). In the GMFCS grade 3 children, no difference was determined in the GMFS-C points (p>0.05), however there were significant improvements in the GMFS-B, D and E values (z=-2.214, p=0.027; z=-2.812, p=0.005; z=-2.201, p=0.028, respectively) and in MAS and GAS (z=-2.530, p=0.011; z=-2.558, p=0.011, respectively). In the GMFCS level 4 children, GMFS-D and E dimensions (z=-2.032, p=0.042; z=-2.032, p=0.042, respectively) and MAS and GAS (z=-2.460, p=0.014; z=-2.714, p=0.007, respectively) improved significantly when compared to baseline values, but no significant difference was observed in values of GMFS-B and C dimensions (p<0.05) (Table 2).

When intra-group comparisons were done according to the CP type, no significant change was observed after treatment in the bilateral spastic children in respect of the GMFS-B and C points (p>0.05), however there were significant improvements in D and E points (z=-2.821, p=0.005; z=-2.403, p=0.016, respectively), and MAS and GAS measurements (z=-3.217, p=0.001; z=-3.100, p=0.002, respectively). No significant change was observed in the unilateral spastic children in

Table 1. The targets of the patients according to the Goal Attainment scale

	Patient	Target
1	A.M.Y.	To sit on the mat for at least 3 secs with the arms free and independent
2	B.E.Ş.	To sit on a chair for at least 10 secs with the arms free and independent
3	B.K.	To stand for at least 20 secs with the arms free and independent
4	C.B.	To sit on a chair for at least 10 secs with the arms free and independent
5	D.D.	To stand supported by 1 hand
6	E.D.	To walk 10 steps forward and turn 180°
7	E.C.İ.	In a standing position supported by 1 hand, to raise 1 foot from the floor and hold this position for at least 3 secs
8	E.M.Ç.	In a full kneeeling position, to advance 4 steps with the arms free
9	E.A.	To come to a half-kneeling position from a full kneeling position and hold this position for at least 10 secs
10	E.B.	To sit on the mat for at least 3 secs with the arms free and independent
11	E.H.U.	To stand for at least 20 secs with the arms free and independent
12	E.K.	To extend one arm forward while in a crawling position
13	E.K.	To come to a half-kneeling position from a full kneeling position and hold this position for at least 10 secs
14	F.A.K.	To come to a half-kneeling position from a full kneeling position and hold this position for at least 10 secs
15	H.İ.	To sit on the mat for at least 3 secs with the arms free and independent
16	H.G.	To stand independently and raising 1 leg, hold this position for at least 10 secs
17	H.C.U.	To step over an obstruction at ankle level
18	M.K.	To stand for at least 20 secs with the arms free and independent
19	M.C.K.	To stand for at least 20 secs with the arms free and independent
20	R.Ö.	To stand independently and raising 1 leg, hold this position for at least 10 secs
21	S.A.	In a crawling position, to make reciprocal forward crawling
22	S.G.E.	To walk 10 steps forward
23	S.E.	To walk 10 steps forward and turn 180°
24	S.K.	To walk 10 steps forward
25	Ş.K.	To sit on the mat for at least 3 secs with the arms free and independent
26	T.T.	To sit on the mat for at least 3 secs with the arms free and independent
27	T.Ş.	In a crawling position, to make reciprocal forward crawling
28	V.Y.	To step over an obstruction at ankle level

respect of the GMFS points, MAS and GAS (p>0.05). In the mixed type spastic children, no difference was determined in the GMFS-B, C and E points and MAS (p>0.05). A significant increase was determined in the GMFS-D points and in GAS (z=-2.207, p=0.027; z=-2.121, p=0.034, respectively) (Table 3).

When inter-group comparisons were performed after the RR, no difference was determined between the GMFCS groups in respect of GAS, MAS and GMFS-B, C and E points (p>0.05), however, GMFS-D values were significantly different (chi-square=16.564, p<0.001). The increase in the GMFS-D points in the level 2 and level 3 children was greater than the increase in those at grade 4 (z=-2.214, p=0.027; z=-3.915, p<0.001, respectively) (Table 2). No statistically significant difference was determined between the CP type groups in respect of all the GMFS points, MAS and GAS (p>0.05) (Table 3).

Discussion

The aim of this study was to evaluate the response to RR in respect of motor function development in children with CP of different types and with different levels of motor function. At the end of treatment, while no change was observed in the GMFS points of the level 2 children, an increase was determined in the GMFS-B, D and E points of the level 3 children, and in the GMFS-D and E points of the level 4 children. No change was seen in MAS and GAS in level 2 children, whereas a decrease in MAS and an increase in GAS were seen in level 3 and level 4 children. In the group comparisons, the increase in the GMFS-D points of the level 2 and 3 children was greater than in the grade 4 children.

There have been conflicting reports related to the efficacy of RR applied to children with CP at different gross motor function levels (7,13). van Hedel et al. (7) applied a mean of 20 RR sessions in addition to a regular physiotherapy program in a group of children with CP aged 4-20 years, comprising 15% level 2, 23% level 3, and 29% level 4. They reported that while there was no development in level 2 children, significant improvements were observed in GMFS-D and E points of level 3 and 4 children, without significant differences between the groups. Borggraefe et al. (13) applied 12 sessions of RR and determined a greater development in GMFS-D in level 1 and 2 children compared to those of level 3 and 4. In a study by Willoughby et al. (16), it

Table 2. Improvement in spasticity, Gross Motor Function Measure, and Goal Attainment scale in different levels of Gross Motor Funtion Classification System

		Gross Motor Function Classification System								
		Level 2 n=3 median (min-max)			Level 3 n=10 median (min-max)			Level 4 n=15 median (min-max)		
Age, year		12 (10-13)			11 (8-14)			11 (6-16)		
Number of sessions		26 (26-31)			31.5 (25-32)			28 (20-32)		
Duration per session, min		37 (33-40)			39.5 (33-54)			34 (26-44)		
		BT	AT	D	BT	AT	D	BT	AT	D
MAS		2 (1-2)	1 (1)	-1 (-1-0)	2 (1-3)	1 (1-3)§	-1 (-1-0)	2 (1-3)	1 (1-3)§	0 (-1-0)
GAS		-2 (-2)	-1 (-2-1)	1 (0-1)	-2 (-2)	-1 (-2-1)§	1 (0-2)	-2 (-2)	-1 (-2-1)§	1 (0-2)
GMFM (%)	B	88 (77-100)	100 (93-100)	16 (0-16)	96 (75-100)	100 (76-100)§	1 (0-13)	84 (24-100)	86 (24-100)	0 (-5-7)
	C	100 (70-100)*	100 (80-100)	4 (0-10)	96 (66-100)*	100 (68-100)	0 (0-2)	52 (0-96)*†‡	51 (0-96)	0 (-11-2)
	D	64 (23-74)*	76 (27-100)	4 (2-36)†	37 (2-56)*	56 (10-71)§	7 (4-58)‡	2 (0-20)*†‡	2 (0-22)§	0 (0-5)*†
	E	66 (17-73)*	67 (18-73)	1 (0-1)	21 (2-54)*	23 (5-57)§	2 (-2-19)	0 (0-20)*†‡	0 (0-24)§	0 (0-11)

*Kruskal Wallis, †Mann-Whitney U, level 2-4, ‡Mann-Whitney U, level 3-4, §Wilcoxon, p<0.05

BT: Before treatment, AT: After treatment, D: Difference, MAS: Modifiye Ashwort scale, GAS: Goal Attainment scale, GMFS: Gross Motor Function scale, B: Sitting dimension, C: Crawling- kneeling dimension, D: Standing dimension, E: Walking, running, jumping dimension, min: Minimum, max: Maximum

was reported that the children with more functional disability were more likely to benefit from RR.

In studies that have compared RR with conventional PT, different results have been reported in respect of efficacy (4,10,11,22,23). In a study which compared 20 sessions of RR and PT in bilateral spastic, level 2 children aged 8-10 years, improvement was recorded in the RR group in GMFS-D and E points (4). Another study found no difference between a PT group and an RR group in kinematics and step length, step width and walking speed measurement in level 2-3 CP children aged 6-13 years with spastic diplegia (10). Level 2-4, bilateral spastic CP children aged 4-12 years were compared as a hospitalised group applied with 20x45-min sessions of PT and an outpatient group applied with 12x60-min sessions of RR, and no difference was determined between the groups, with a similar increase in walking speed and GMFS-D points in both groups (11). In level 1-3, bilateral spastic CP children aged 4-17 years, treatment was applied for 4-10 weeks at a frequency of 4-10 sessions per week and no difference was determined between the RR, PT and PT+RR protocols. Similar results were determined to have been obtained from the robotic application and the physiotherapy, and it was concluded that a single application was more beneficial than combined applications, with reported improvements in GMFS-D and E points in all groups (22). In a study by Romei et al. (23), 20 sessions of RR and PT were compared with RR alone in bilateral spastic CP children, and it was reported that both groups improved and there was no difference between the groups in respect of the improvement in gross motor function.

van Hedel et al. (7) determined a strong relationship between the GMFS-E dimension and the total number of treatment sessions in level 2 CP children. In that study, although not significant, the total number of RR sessions was higher, and the duration of the sessions was longer in grade 2 and 3 children. Despite the lack of studies directly comparing RR treatment doses, that children who were more affected in respect of motor function were likely to benefit more from the application of a greater total number of sessions and longer session duration (7). Researchers have emphasised that more severely impaired children benefit more from a greater number of sessions, and longer walking distance and duration of the sessions, while lesser affected children benefit from high

Table 3. Improvement in spasticity, Gross Motor Function Measure, and Goal Attainment scale according to cerebral palsy type

		Bilateral spastic n=17 median (min-max)			Unilateral spastic n=6 median (min-max)			Mixed n=4 median (min-max)		
Age, year		12 (6-16)			10 (8-13)			11 (7-16)		
Number of sessions		30 (20-32)†			26 (21-32)			22.5 (21-27)*†		
Duration per session, min		37 (29-54)			36.5 (32-44)			32 (26-39)		
		BT	AT	D	BT	AT	D	BT	AT	D
MAS		2 (1-3)	1 (1-3)	-1 (-1-0)‡	2 (1-2)	1 (1-2)	-0.5 (-1-0)	2.5 (2-3)	2.5 (1-3)	0 (-1-0)
GAS		-2 (-2)	-1 (-2-1)	1 (0-2)‡	-2 -2 (-2)	-1 (-2-1)	1 (0-1)‡	-2 (-2)	-1.5 (-2-0)	0.5 (0-2)
GMFS (%)	B	86 (24-100)	87 (24-100)	0 (-5-13)	92,5 (77-100)	100 (90-100)	2.5 (0-16)	94 (44-97)	94.5 (44-100)	0.5 (0-3)
	C	76 (0-100)	75 (0-100)	0 (-11-2)	91 (46-100)	91 (46-100)	0.5 (0-10)	55 (0-100)	56 (0-100)	0 (0-2)
	D	10 (0-56)*†	15 (0-71)	4 (0-58)‡	58 (15-100)*†	58 (15-100)	4 (1-36)‡	10 (0-43)*	11 (0-48)	1 (0-5)
	E	11 (0-47)	11 (0-57)	1 (-2-19)‡	29.5 (0-73)	32.5 (0-73)	1 (0-4)	6 (0-54)	6.5 (0-56)	0.5 (0-2)

*Kruskal-Wallis; †Mann-Whitney U, ‡Wilcoxon, p<0.05

BT: Before treatment, AT: After treatment, D: Difference, MAS: Modifiye Ashwort scale, GAS: Goal Attainment scale, GMFS: Gross Motor Function scale, B: Sitting dimension, C: Crawling- kneeling dimension, D: Standing dimension, E: Walking, running, jumping dimension, min: Minimum, max: Maximum

intensity programs of shorter duration (24,25).

In the current study, while no change was determined in GMFS points, MAS and GAS in unilateral spastic children, an increase was determined in GMFS-D and E and an improvement in MAS and GAS measurements in bilateral spastic children. In the mixed type children, an increase was determined in GMFS-D points and GAS. No difference was determined in the GMFS, MAS and GAS between the CP types. As there is no previous study in literature that has evaluated the efficacy of RR in different CP types, no comparison could be made. Although there was no difference between the CP types in respect of MAS, the MAS median value was found to be higher in the bilateral spastic and mixed type groups. The improvement in motor function in the bilateral spastic and mixed type groups can be considered to be due to a reduction in partial spasticity, associated with the negative effect of spasticity on gross motor function (26).

It has been emphasised that for there to be benefits of robotic walking training in respect of improvements in walking speed, resistance and gross motor functions in children with CP, the program should be applied at a frequency of 4 days per week with sessions of at least 30 mins (30) and it has been stated that strong evidence is required to determine the role of robot-assisted walking in CP children (10,15).

The primary limitation of the current study was the low sample size of different motor function grades and different CP types, and that there was no control group. Second is that the anthropometric details of the children and energy consumption were not recorded as it has been previously reported that anthropometric differences affect gait kinetics and motor behaviour (3). It has been emphasised that a reduction in energy consumption is related to a reduction in contractions of spastic muscles and a more effective gait pattern (3). A third limitation was that details could not be obtained of the reliable application of the RR as it was implemented at a different centre.

Conclusion

In conclusion, although several methodological limitations prevent definite conclusions, a number of potential clinical implications emerge from this study. Our results showed that RR application is beneficial for improving standing activities in bilateral spastic children with CP at GMFCS level 2 and 3. Further prospective studies are needed to confirm these results in larger groups of patients to improve the evidence-based application of RR.

Ethics

Ethics Committee Approval: The Ethics Committee of the University of Health Sciences, Antalya Training and Research Hospital approved the study (approvel number: 2015-029).

Informed Consent: As this was a resrospective study, there is no informed consent.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: M.B.F., N.F.T., T.Ç., H.A., Concept: N.F.T., C.M.A.Ç., Ş.K.D., Design: N.F.T., C.M.A.Ç., H.A., T.Ç., Data Collection or Processing: C.M.A.Ç., H.A., Ş.K.D., Analysis or Interpretation: M.B.F., N.F.T., Literature Search: T.Ç., Ş.K.D., Writing: M.B.F., N.F.T.

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Original Article / Özgün Araştırma

Investigation of Tooth Extraction Reasons in Patients Who Applied to a Dental Faculty

Bir Diş Hekimliği Fakültesine Başvuran Hastalarda Diş Çekimi Nedenlerinin Araştırılması

Melek Taşsöker[1], Dilek Menziletoğlu[2], Funda Baştürk[2], Said Karabekiroğlu[3], Sevgi Şener[1]

[1]Necmettin Erbakan University Faculty of Dentistry, Department of Oral and Maxillofacial Radiology, Konya, Turkey
[2]Necmettin Erbakan University Faculty of Dentistry, Department of Oral And Maxillofacial Surgery, Konya, Turkey
[3]Necmettin Erbakan University Faculty of Dentistry, Department of Restorative Dentistry, Konya, Turkey

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Anahtar Kelimeler
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Address for Correspondence/Yazışma Adresi: Melek Taşsöker MD, Necmettin Erbakan University Faculty of Dentistry, Department of Oral and Maxillofacial Radiology, Konya, Turkey
Phone : +90 332 220 00 25
E-mail : dntst231@gmail.com
ORCID ID: orcid.org/0000-0003-2062-5713

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Abstract

Objective: This study was aimed to determine the reasons for extraction of permanent teeth in patients who applied to Necmettin Erbakan University Faculty of Dentistry in Turkey.

Materials and Methods: A clinical survey was done for the patients ranging in age from 11 to 79 years that has undergone tooth extraction at department of oral and maxillofacial surgery. The permanent tooth extraction reasons were recorded excluding third molars. Reasons for tooth extraction were assigned to eight groups: tooth caries, periodontal disease, orthodontic, endo-perio lesions, preprosthetic, patients request, trauma and other reasons. Additionally, frequency of tooth brushing and dental visit, sociodemographic datas such as age, gender, residence place, education and income level were recorded for each participant. Obtained data were statistically analyzed by using descriptive statistics and chi-square test with a significance level at $p<0.05$.

Results: A total of 792 teeth were extracted from 487 patients. Males were 50.7% while females formed 49.3%. The reasons for extractions were: tooth caries 39.6%, periodontal disease 31.2%, orthodontic 1.8%, endo-perio lesions 17.5%, preprosthetic 6.8%, patient request 2.1%, trauma 0.8% and 0.2% other reasons. The tooth type most frequently extracted was the first left mandibular molar. The tooth type least frequently extracted was the left mandibular canine.

Conclusion: Both caries and periodontal disease were the main reasons for tooth extraction in this Turkish subpopulation, so that proper oral health system including efficient programs focusing on prevention and treatment of these diseases should be created and developed.

Öz

Amaç: Bu çalışma Necmettin Erbakan Üniversitesi Diş Hekimliği Fakültesi'ne başvuran hastalarda daimi diş çekim nedenlerini saptamayı amaçlamıştır.

Gereç ve Yöntemler: Çalışma, ağız, diş ve çene cerrahisi ana bilim dalında diş çekimi yapılan 11-79 yaş aralığındaki hastalar ile yürütülmüştür. Daimi diş çekim nedenleri kaydedilirken üçüncü molar dişler dahil edilmemiştir. Diş çekim nedenleri: Diş çürükleri, periodontal hastalık, ortodontik, endo-perio lezyonlar, preprostetik, hasta isteği, travma ve diğer nedenler olmak üzere sekiz kategoriye ayrılmıştır. Ek olarak, diş fırçalama ve diş hekimi ziyareti sıklığı, yaş, cinsiyet, yaşanılan yer, eğitim

ve gelir seviyesi gibi sosyodemografik bilgiler de her hasta için kayıt altına alınmıştır. Elde edilen veriler tanımlayıcı istatistikler ve ki-kare testi ile p<0,05 düzeyinde analiz edilmiştir.
Bulgular: Dört üz seksen yedi hastadan 792 diş çekilmiştir. Erkekler çalışmanın %50,7'sini, kadınlar %49,3'ünü oluşturmaktadır. Diş çekim nedenlerinde diş çürüğü %39,6, periodontal hastalık %31,2, ortodontik nedenler %1,8, endo-perio lezyonlar %17,5, preprotetik nedenler %6,8, hasta isteği %2,1, travma %0,8 ve diğer nedenler %0,2 olarak dağılım göstermiştir. En sık çekimi yapılan diş sol birinci mandibular molar iken en az çekim sol mandibular kaninde olmuştur.
Sonuç: İncelenen Türk alt popülasyonunda çürük ve periodontal hastalık diş çekimlerinin ana nedenleri olduğundan bu hastalıkların önlenmesi ve tedavi edilmesine odaklanan etkili programları içeren uygun bir ağız sağlığı sistemi oluşturulmalı ve geliştirilmelidir.

Introduction

Oral health requires the permanent teeth retention as long as possible because the teeth are important not only for functional reasons but also esthetics (1,2). Tooth extraction should only be performed if heavily recommended as a part of dental treatment (1). Tooth extraction can be related to many factors mainly classified into clinical and non-clinical. Clinical factors are dental caries, periodontitis, dental trauma, eruption problems (impactions, pericoronitis), prosthodontic reasons and orthodontic reasons. Nonclinical factors include socioeconomic demographic characteristics, lack of education, oral hygiene habits, lack of awareness and patients demand of tooth extraction even after restorative treatment (2). Takala et al. (3) stated that older, less well-educated, poorer, rural and male population lost teeth more frequently. Several studies have been conducted worlwide on this issue and most of the studies indicated caries is the major cause of tooth extraction. Additionally, with aging the causes of extraction differs and periodontitis becomes the leading cause (especially after years of 40) (2,4-8). Caries and periodontal diseases are looks like the two main reasons of tooth extraction (4,5,9). Tooth loss is in close relation to financial and economic situations of the patients (8). Populations with poorer socioeconomic profiles have shown higher prevalence of tooth loss (10). Turkey is a country in development progress and developing countries have the limitation of health resources. This situation may lead to prefer simple dental care procedures like extractions (2). The lower prevalence of tooth loss in developed countries can be explained by preventive programs and higher accessibility to the oral health care (10). An understanding of the tooth extraction reasons is vitally important to improve oral health (11). There have been no recent studies regarding the current reasons for dental extractions in Turkey. The aim of this study was to find out the reasons for the extraction of permanent teeth in patients operated in the Department of Oral and Maxillofacial Surgery in a Dental Faculty.

Materials and Methods

A clinical survey was done for the patients that has undergone tooth extraction at Department of Oral and Maxillofacial Surgery in Necmettin Erbakan University Faculty of Dentistry between 2016-2017 years. Research protocol was approved by the Ethical Committee (project no: 2016/006). Four hundred eighty seven patients were included in the study ranging in age from 11 to 79 years. Patients were divided into seven age subgroups (Table 1). Out of 487 patients 247 were male and 240 were female. An informed and written consent was taken before participating the study. The permanent tooth extraction reasons were recorded excluding third molars. Because the study range of age is not reliable for presence of third molars and they have congenitally missing and/or impacted nature. The diagnosis was done based on both clinical and radiographic examination by one investigator. Reasons for tooth extraction were assigned to eight groups: tooth caries, periodontal disease, orthodontic, endo-perio lesions, preprosthetic, patients request, trauma and other reasons (local pathology, tooth impaction, and iatrogenic). Additionally, frequency of tooth brushing and dental visit, sociodemographic data such as age, gender, residence place, education and income level were recorded for each participant. Data analysis were performed by SPSS ver. 21.0 (Chicago, IL, USA). Obtained data were statistically analyzed by using descriptive statistics and chi-square test with a significance level at p<0.05.

Results

A total of 792 teeth were extracted from 487 patients with a mean of 1.62 extraction per person during the study and 6.34 teeth were missing for per patient. Of the 792 teeth extracted, 336 were from females and 456 were from males. Of the 792 teeth extracted, 530 were from the participants of age over 40 years and 262 were from the participants of age under 40 years. The patients were divided into seven age subgroups and the distribution of the extracted teeth according to age subgroups were given in Table 1. Mean age of the study population was 43.46±14.95. Males were 50.7% while females formed 49.3% of the sample. Some sociodemographic data such as age, gender and education were given in the tables (Tables 1, 2). The reasons for extractions were: tooth caries 39.6%, periodontal disease 31.2%, orthodontic 1.8%, endo-perio lesions 17.5%, preprosthetic 6.8%, patient request 2.1%, trauma 0.8% and 0.2% other reasons (tooth impaction for one patient) (Figure 1). The reasons for tooth extraction were about the same rates in males and females and there was no statistically significant difference (p>0.05, p=0.217) (Table 3). Tooth caries was responsible for the majority of the extractions in both males and females in two age groups (Table 3). Significant difference was seen in the reasons of tooth extraction between seven age subgroups (p<0.001, p=0.000). The rate of periodontal disease increased as the tooth caries rate decreased in the age subgroups of over 40 years. The rate of preprosthetic extractions increased in the age subgroups of over 40 years and there was no extraction for orthodontic reasons in the age groups of above 30 years (Table 4). The distribution of extractions according to tooth type is given in the table (Table 5). The tooth type most frequently extracted was the first left mandibular molar. The tooth type least commonly extracted was the left mandibular canine. Tooth type had a significant effect on the extraction reasons (p<0.05). The maxillary and mandibular anterior teeth group were commonly extracted with the reason of periodontal diseases while posterior teeth group were commonly extracted with tooth caries reason. 93.6% of the study sample constituted of the urban population. There was no relationship between residence place and extraction reasons (p>0.05, p=0.286). The majority of the patients visit their dentist “in case complaint” (95.7%) and the remainig portion (4.3%) visits “biennially” or “once a year”. The frequency of dental visit had no significant effect on the extraction reasons (p>0.05, p=0.103). The majority of the patients (70.6%) had low income and the remaining part consisted of medium and high income level (29.4%). There was a statistically significant difference between income level and extraction reasons (p<0.05, p=0.023). As the income level rised the number of extracted teeth

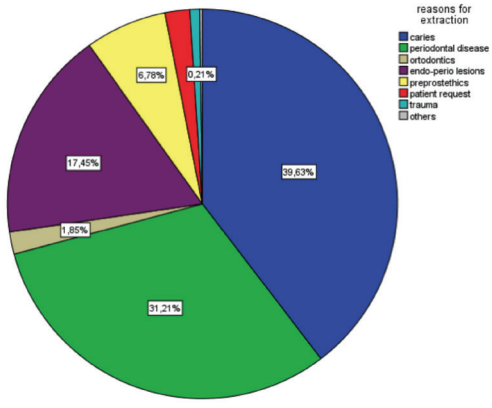

Figure 1. The distribution of the study sample based on the tooth extraction reasons

Table 1. Socio-demographic characteristics of the study population

Age groups (years)	Number of patients	Male/female number	Number of extracted teeth	Extraction per person	Mean (years)	Standard deviation (years)
11-20	24	7/17	24	1	17.83	2.54
21-30	82	43/39	98	1.19	25.65	2.99
31-40	109	61/48	140	1.28	35.11	2.73
41-50	110	52/58	149	1.35	45.53	3.04
51-60	92	46/46	144	1.56	55.25	2.67
61-70	54	28/26	113	2.09	65.04	3.77
71-79	16	10/6	124	7.75	75.38	5.60
Total	487	-	792	-	-	-

decreased in all extraction reason groups. Thirty nine percent of the 487 patients had the habit of tooth brushing before asleep. The habit of tooth brushing before asleep, the level of education and the frequency of tooth brushing had a significant effect on tooth extraction (p<0.001) (Table 6). As the level of education, frequency of tooth brushing and tooth brushing habit before asleep increased, the number of extracted tooth prone to decrease in all reason groups. The tooth brushing frequency according to extraction reasons of the individuals were given in the Table 7.

Table 2. The distribution of the patients based on education

Education	Number of patients	Percent (%)
Illiterate	12	2.5
Primary school	285	58.5
High school	77	15.8
University	113	23.2
Total	487	100.0

Table 3. Tooth extraction reasons according to gender

		Tooth extraction reasons								Total
		Caries	Periodontal disease	Ortodontics	Endo-perio lesions	Preprostethics	Patient request	Trauma	Others	
Gender	**Male**	103	74	5	44	17	1	3	0	247
	Female	90	78	4	41	16	9	1	1	240
Total		193	152	9	85	33	10	4	1	487

Table 5. The distribution of extractions according to tooth type

Tooth type	% of extraction	Tooth type	% of extraction
11	1.7	**31**	3.8
12	2.2	**32**	3.9
13	2.1	**33**	0.8
14	4.7	**34**	2.3
15	3.9	**35**	2.8
16	5.8	**36**	7.7
17	5.4	**37**	6.6
21	1.9	**41**	4.4
22	2.5	**42**	3.7
23	1.4	**43**	1.5
24	4.6	**44**	2.5
25	3.4	**45**	1.7
26	4.4	**46**	4.8
27	4.6	**47**	4.9

Table 6. P values of the evaluated parameters

Parameters	p values
Education	0.000**
Income level	0.023*
Frequency of tooth brushing	0.000**
Brushing teeth before asleep	0.000**
Residence place	0.286
Frequency of dental visit	0.103

*Significance level is p<0.05, **Significance level is p<0.001

Table 4. Tooth extraction reasons according to age

		Tooth extraction reasons								Total
		Caries	Periodontal disease	Ortodontics	Endo-perio lesions	Preprostethics	Patient request	Trauma	Others	
Age (years)	**11-20**	13	0	5	5	0	0	1	0	
	21-30	45	7	4	20	1	3	1	1	
	31-40	51	28	0	25	2	2	1	0	
	41-50	41	39	0	23	5	2	0	0	
	51-60	27	40	0	10	14	1	0	0	
	61-70	12	27	0	2	10	2	1	0	
	71-79	4	11	0	0	1	0	0	0	
Total		193	152	9	85	33	10	4	1	487

Discussion

Our study demonstrated that the tooth caries was the leading reason with 39.6% of all reasons followed by periodontal disease 31.2% of all reasons of tooth extractions in accordance with previous studies (1,3-5,7,9-15) given in the Table 8. Great variation exists in the frequency and causes of tooth extraction in different countries (16). For example, caries is responsible for majority of the extractions in a wide range from 25% (3) to 70.3% (15) in the literature. This situation can be explained with sample size, study design, geographic and genetic diversities (4,5,17). Genetic factors may affect the type of saliva and tooth morphology. Geographic and ethnic differences may affect the dietary habits (18). Additionally, education, economical condition, dental care behavior and lifestyle factors such as smoking, etc. should be considered (8,19). Our study showed that tooth caries persisted as the major tooth extraction reason, but the rate of periodontal disease increased in older age group (>40 years). The number of teeth extracted teeth per person was dramatically increased in the age group of over 70 years (7.75) and 68% of those teeth was extracted with periodontal reasons. Tooth caries is a disease of young (1). In young age, proper oral hygiene cannot be achieved along with unhealthy oral habits (2). The prevalence of tooth extraction with the reason of caries decreased possibly due to stabilisation of oral hygene and nutrition habits in older age (20). Calculus deposition increases with age and calculus leads to periodontal destruction (7). The effects of periodontal disease are chronic and cumulative in nature and the extractions with periodontal reasons increases later in life (21). These results are in consistent with Yasser et al. (4), Thomas and Al-Maqdassy (18), Hull et al. (7) and Preethanath (22) while incompatible with Alesia and Khalil (16) and Murray et al. (23).

Table 7. The frequency of the tooth brushing of the patients according to tooth extraction reasons

Tooth extraction reasons	Frequency of tooth brushing				Total
	Sometimes	Twice a week	Everyday	Twice a day	
Caries	85	26	60	22	193
Periodontal disease	72	12	48	20	152
Ortodontics	0	0	1	8	9
Endo-perio lesions	19	5	35	26	85
Preprostethics	14	3	14	2	33
Patient request	2	1	4	3	10
Trauma	1	1	0	2	4
Others	0	0	0	1	1
Total	193	48	162	84	487

Table 8. Studies in the literature

Author	Population	Sample size	Extracted for caries	Extracted for periodontal disease
Chestnutt et al. (11)	Scotland	613	51%	21%
Da'ameh (1)	Afghanistan	123	59.2%	35.3%
Al-Sharafat and Al Negrish (12)	Jordan	1030	39.7%	20.9%
Yasser et al. (4)	Pakistan	178	52.6%	26.4%
Al-Shammari et al. (5)	Kuwait	1604	43.7%	37.4%
Richards et al. (9)	Wales	417	59%	29.1%
Montandon et al. (10)	Brazil	439	38.4%	32.3%
Hull et al. (7)	United Kingdom	389	37%	29%
Hassan (13)	Libya	600	54%	41%
Anand et al. (14)	India	635	44.6%	33.2%
Caldas (15)	Brazil	404	70.3%	15.1%
Takala et al. (3)	Finland	233	25%	20%

Only 9 teeth were extracted with orthodontic reasons in this study among people younger than 30. Alesia and Khalil (16) found that orthodontic reasons for tooth extraction was the second major reason for extractions in Saudi population. This result could be explained with the increasing interest in the esthetic considerations (16). Murray et al. (23) found that extraction with periodontal diseases accounted for more than caries in Canada population. The average age of the sample should be considered as an anohter affecting parameter leading different results.

The results of the present study indicated that gender had no effect on the tooth extraction in contrast to the study of Hassan (13). Hassan (13) claimed that this distribution could be explained by differences between genders with regard to the importance of aesthetics. Lesolang et al. (21) suggested that this situation may be due to the differences in cariogenic food affinity and treatment seeking among two genders. The tooth type most frequently extracted was the first left mandibular molar in this study. First molars are the first erupted teeth and they are exposed to local contributing factors leading to caries and early tooth loss (24). Mandibular anterior teeth are less susceptible and relatively resistant to caries than other teeth (1,5,17) and our results indicated that the tooth type least commonly extracted was the left mandibular canine. Similar findings were reported by Mohammed (25). Montandon et al. (10) suggested that controversial findings between studies could be explained by differences in the characteristics of the study population, cultural beliefs, and socioeconomic characteristics. Poor socioeconomic condition causes difficulty in reach to dental care and most people exposed to extraction of their teeth. It is mentioned that tooth loss is a socio-behavioral issue (19). Haugejorden et al. (26) concluded that demographic, behavioural and attitudinal factors had a statistically significant effect on tooth loss. Our results revealed that as the level of education, income, frequency of tooth brushing and tooth brushing habit before asleep increased, the number of extracted tooth decreased in all reason groups. Tooth loss is an indicator of poor oral health (27). The lack of education and low socioeconomic status can attribute the tooth loss increase (18,22). People with higher level of education and economical status may be more likely to consider retaining their teeth and regard the extraction as a last choice (27,28). Poor socioeconomic profile makes difficult to access to prevention and care services (24). Preventive programs are needed especially among people at low socioeconomic status (18). A couple of study conducted in Turkey on this issue up to day. Görgün et al. (29) studied on 468 patients in Ankara region. Their results showed that 45.7% of tooth extraction were due to caries, 31% were due to periodontal reasons. Ceylan et al. (30) studied in Samsun and Erzurum regions with 200 patients and found similar results. In anohter study carried out in Hacettepe University, Hayran et al. (28) classified 850 patients in two age groups, under and above the age of 25 years. The major extraction reason was caries in the age group of under the age of 25 years and periodontal reasons were main causes of extractions in the age group of above 25 years. This study evaluated people who sought dental treatment in a university hospital therefore the sample could not reflect the whole population. Within the limitations of the present study our findings indicated the caries and periodontal problems are major public oral health issue. Besides, socioeconomic and behavioral factors such as education, income and tooth brushing were found to be influental on tooth loss.

Conclusion

Both caries and periodontal disease were the main reasons for tooth extraction in this Turkish subpopulation. Proper oral health system including efficient programs focusing on prevention and treatment of these diseases than extraction should be created and developed. Mandatory regular dental checkups must be provided by the government for diagnosing caries at an early stage before tooth extraction. This will reduce the prevalence of dental caries and furthermore decrease the future costs of surgical, restorative and prosthetic treatments. Further larger studies including all regions of Turkey are advised to investigate potential difference of tooth extraction reasons.

Ethics

Ethics Committee Approval: Research protocol was approved by the Necmettin Erbakan University Ethics Committee (project no: 2016/006).

Informed Consent: An informed and written consent was obtained before participating the study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: D.M., F.B., Concept: M.T., S.K., D.M., Design: M.T., S.K., Data Colletion or Processing: M.T., S.K., D.M., F.B., Analysis or Interpretation: M.T., S.Ş., Literature Search: M.T., Writing: M.T.

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Original Article / Özgün Araştırma

Dental Anxiety in Relationship to Demographic Status and Periodontal Health in Adults

Dental Anksiyetenin Periodontal Sağlık ve Demografik Durum ile İlişkisi

Gülnihal Eren, Oya Türkoğlu

Ege University Faculty of Dentistry, Department of Periodontology, İzmir, Turkey

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Address for Correspondence/Yazışma Adresi:
Gülnihal Eren MD, Ege University Faculty of Dentistry, Department of Periodontology, İzmir, Turkey
Phone : +90 536 898 94 34
E-mail : gulnihal_karasu@hotmail.com
ORCID ID: orcid.org/0000-0003-1148-2802

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Abstract

Objective: Dental anxiety is a major complication for many patients and practitioners. Dental fear often results in poor oral health in regard to poor cooperation. The aim of the present study was to determine the dental anxiety and its relation to socio-demographic status and periodontal health in adults.

Materials and Methods: In this cross-sectional study, a total of 187 patients were asked to complete a questionnaire consisted of the questions gathering information on sex, age, education level, income level, smoking habits and the last dental visit. The questionnaire also included Modified Dental Anxiety scale (MDAS) administered in Turkish language. The oral health status was determined with Community Periodontal index (CPI).

Results: Based on MDAS scores, 54% of the subjects had mild anxiety, 41.7% had moderate anxiety, and 4.3% had severe anxiety. Anxiety was affected by age and gender ($p<0.05$), but monthly income, education level, or smoking status had no effect on dental anxiety ($p>0.05$). Participants with higher CPI scores had significantly higher dental anxiety compared to those of lower CPI scores ($p<0.05$).

Conclusion: Encouragement of young individuals for regular dental visits since childhood would help to lower the dental anxiety. Frequent dental visits might prevent the negative dental experiences and contribute to decrease the dental fear.

Öz

Amaç: Diş hekimi korkusu nedeniyle hastaların gerekli diş tedavilerinden kaçınması ağız sağlığını olumsuz yönde etkiler. Bu çalışmanın amacı dental anksiyete ile sosyo-demografik durum ve periodontal sağlık arasındaki ilişkinin araştırılmasıdır.

Gereç ve Yöntemler: Bu kesitsel çalışmaya dahil edilen 187 hastadan cinsiyet, yaş, eğitim düzeyi, gelir düzeyi, sigara içme alışkanlıkları ve son diş hekimi ziyareti ile ilgili ankete yanıt vermeleri istendi. Hastalara yöneltilen ankette Türkçe olarak düzenlenmiş Modifiye Dental Anksiyete ölçeği (MDAS) de yer aldı. Periodontal durum [Community Periodontal index (CPI)] ile belirlendi.

Bulgular: MDAS düzeylerine göre, olguların %54'ünde hafif anksiyete, %41,7'sinde orta düzeyde anksiyete ve %4,3'ünde ciddi anksiyete gözlendi. Anksiyetenin, yaş ve cinsiyete bağlı olarak değiştiği ($p<0,05$), ancak aylık gelir, eğitim düzeyi veya sigara içme durumundan etkilenmediği belirlendi ($p>0,05$). CPI skoru daha yüksek olan bireylerde MDAS düzeyleri, düşük CPI skoruna sahip bireylere kıyasla, anlamlı derecede yüksek bulundu ($p<0,05$).

Sonuç: Çocukluk döneminden itibaren diş hekimi ziyaretleri için genç bireylerin teşvik edilmesi, dental anksiyeteyi azaltmaya yardımcı olacaktır. Sık diş hekimi ziyareti, olumsuz deneyimleri engelleyebilir ve diş hekimi korkusunu azaltmaya katkıda bulunabilir.

Introduction

Dental anxiety is a common problem for considerable number of patients and often results in inadequate oral health by less frequent dental visit, avoidance of dental treatment and poor cooperation (1-6). Several studies have evaluated the prevalence of dental anxiety range approximately 5% to 30% depending on the population and measurement technique used (4,6-8). Liu et al. (6) assessed dental anxiety among Chinese population and reported that 5% were suffering from dental phobia. In a Spanish population Rodriguez Vazquez et al. (8) assessed the stress before dental treatment and found that 10% patients scored high values stress. Thomson et al. (7) investigated New Zealand adults with a postal survey and observed that dental anxiety was reported by 20.8 per cent of respondents. In Turkish population, approximately 21%-24% of individuals experienced dental anxiety (4,9,10). The etiology of dental anxiety is a multidimensional real or imaginative stimulus that leads to development of fear (11). It is likely to have been created by several factors such as general fearfulness, past traumatic experiences and negative information based on narratives offered by family or social environment (12,13). People with high levels of dental anxiety might neglect their oral hygiene and have tendency to suspend dental treatment unless they suffer from severe pain. Eventually, dental anxiety becomes a veritable vicious circle that leads to worse oral health and may cause embarrassment associated with deterioration of social life (14). It has been reported that individuals with high dental anxiety more likely to have more missing teeth, more caries and worse oral hygiene in comparison to non-anxious individuals (15,16). Self-reported questionnaires and anxiety rating scales place different degrees of emphasis on dental fear, which is expressed as changes in thoughts, physiological state and behavior by the population (17). These dental anxiety questionnaires show adequate levels of internal consistency (10). Modified Dental Anxiety scale (MDAS) is a quick and brief, 5 item questionnaire adapted from Corah's Dental Anxiety scale (DAS) (18) developed by Humphris et al. (19). An advantage of MDAS is that, it is cost effective instrument for population-based research. Also, MDAS was developed to improve validity of DAS by adding a question about administration of local anesthetic (1). MDAS has been found reliable and valid cross culturally and has been translated into different languages including Turkish (10). Individuals with periodontal disease are likely to report negative impacts in their oral health and express high general anxiety (20). Anxiety, depression and stress are not yet confirmed as definite risk factors of periodontal disease, but they are considered as potential factors affecting the occurrence, development and prognosis of periodontal disease (21,22). Limited number of studies has been performed to investigate the relationship between dental anxiety and periodontal status in Turkey up to now (4,23-25). As periodontal health status is an important factor affecting dental fear (26,27) we hypothesized that greater indications of periodontal disease [i.e., higher Community Periodontal index (CPI) scores] were expected to be related to higher dental anxiety. Therefore, in the present study it is aimed to determine dental anxiety and its relation to demographic and periodontal status of patients who referred to Ege University Faculty of Dentistry.

Materials and Methods

Patient's Recruitment

This cross-sectional study was conducted among a sample of 187 patients attending Ege University Faculty of Dentistry, in the period spanning from September 2014 to March 2015. The purpose and procedures were fully explained to all participants prior to participation and written informed consent was obtained from all those wishing to participate in accordance with Helsinki Declaration. This study was reviewed and approved by the Ethical Committee of Ege University Faculty of Medicine (approval no: 15-9.1/13). Inclusion criteria were age equal to or over 18 and agreement to participate in the study. Those who reported history or undergoing of psychological therapy, presented illiteracy and non-cooperation or took sedative agents 3 days before the survey were excluded from the study.

Data Collection and Questionnaires

Initially, all patients were asked to fill a questionnaire. The questionnaire consisted of two sections. The first section contained questions gathering information on sex, age, education level, income levels, smoking habits and when they had last visit to the dentist. In the second section of the questionnaire, in order to assess dental anxiety, the patients were asked to complete MDAS administered in Turkish language (10). This scale includes 5 brief multiple-choice questions. And each question has a consistent answering scheme ranging from "not anxious" with a value of 1 and "extremely anxious" with a value of 5. Also, periodontal status of the subjects was evaluated using CPI (28). The higher CPI scores refer the worsening periodontal status. One calibrated examiner (G.E.) was performed CPI measurements through examination. The intra-examiner reproducibility of the researcher for CPI measurements was evaluated with a manual periodontal probe, and the interclass correlation coefficient was 88%.

Statistical Analysis

Differences between categorical variables were compared by using a chi-square or Fisher's exact test. Adjustment for gender has been performed for statistical analysis. The Shapiro-Wilk test was used to determine whether data were distributed normally. Data was not normally distributed, so group comparisons were performed by Mann-Whitney U test. Statistical analyses were performed using a statistical package (SPSS Inc., Ver. 20.0, Chicago, IL, USA). Differences were considered significant when p value was <0.05.

Results

Demographic characteristics of the patients are presented in Table 1. The study population comprised 110 females and 77 males (mean age 38±13 years, age range, 20 to 69 years). Mean anxiety level of the study subjects was 10.5±4.18. Based on MDAS scores, 54% of the subjects were identified to have mild anxiety (5-10 total score), 41.7% were moderately anxious (11-18 total score), and 4.3% were suffering from high dental anxiety or dental phobia (19-25 total score). The results of the present study demonstrated that number of females who had moderate dental anxiety was significantly higher than males (p=0.04). Similarly, older subjects had significantly lower levels of dental anxiety than younger participants (p<0.001). Dental anxiety was not affected by monthly income, education level (p>0.05). The results also exhibited that dental anxiety was not related with smoking status of the study participants (p>0.05). There was no significant difference in dental anxiety between participants with and without systemic disease (p>0.05). Dental anxiety of participants who visited the dentist in last one year was not different from the other participants who did not visit the dentist (p>0.05). Participants with higher CPI scores had significantly higher dental anxiety compared to those of lower CPI scores (p=0.033) (Table 1).

Discussion

This cross-sectional study evaluated the dental anxiety among patients who referred to Ege University Faculty of Dentistry for different dental treatment needs. Our results demonstrated that dental anxiety was related to gender, age and periodontal disease severity, but not with monthly income, education level, smoking and systemic disease status. Having a visit to a dentist in last one year was not found to be associated with dental anxiety. In the present study, the level of high dental anxiety was 4.3%. Similar findings were found in a study by Prathima et al. (29) with 4.4%, Moore et al. (30) with 4.2% and Locker et al. (31) with 4.4% high dental anxiety. However, Humphris et al. (32) found grater percentages of high dental anxiety with 11%. In the present study subjects who referred to a dental school were included, in contrast Humphris et al. (32) used a structured interview on telephone in UK adults. It has been demonstrated that high dental anxiety level was the underlying cause for the avoidance of dental appointments (33). Therefore, selection of the study population from subjects attending dental clinics might be the reason for lower percentages of high dental anxiety as it was demonstrated in the present study. In the present study, the prevalence of dental anxiety was significantly higher in females than males, which was consistent with literature (17,30,34-36). Similarly, in Chinese population Liu et al. (6) stated that women were considered more anxious than men. The difference in dental anxiety between females and males might be possibly due to personality and psychological state, as women are being more likely

to express their fears than men (37). In addition, a physiological research on human responses to pain stimuli has shown that women exhibit lower tolerance to pain than men (38). A significant negative correlation between age and dental anxiety has been repeatedly reported in community samples from developed countries (19,32). Humphris et al. (19,32) reported that younger subjects were more anxious than older ones among English population. In a cross-sectional study, Deogade and Suresan (39) found that younger patients were more anxious compared to their elder counterparts in Indian adult population. Also, Liddell and Locker (40) evaluated the relationship between age and dental anxiety in a Canadian population and stated that older adults reported less painful dental experiences than young adults. Similarly, Yildirim (4) found that young patients had significantly higher scores than others in a Turkish population. Our findings are in accordance with these studies (4,19,32,40). In the present study, younger subjects had significantly higher dental anxiety than older participants. Post exposure to various diseases and treatments, increased ability to cope with negative experiences might be the explanations of not having high dental anxiety for older subjects. Also, high dental anxiety in younger participants could be due to the less experience of the dental instruments compared to older subjects. According to Fardal et al. (26) and Fardal and Hansen (27) periodontal status is an important factor affecting dental fear.

Table 1. Socio-demographic characteristics of participants according to their dental anxiety levels

	Anxiety score mild	Anxiety score moderate	Anxiety score high	p
Total n (%)	101 (54)	78 (42)	8 (4)	
Gender (%)				
Female/male	51/49	70/30	63/37	0.04
Age (%)				
20-29	44	45	11	0.001
30-39	44	50	6	
40-49	48	52	0	
50-59	76	21	3	
60-69	92	8	0	
Monthly income (TL) (%)				0.441
<1000	50	47	3	
1000-2000	58	38	4	
>2000	58	33	9	
Education level (%)				0.989
Elementary school	54	42	4	
Secondary school	51	45	4	
University	57	38	5	
Smoking (%)				0.357
Current	44	53	3	
Non-smoker	59	37	4	
Former smoker	59	35	6	
Systemic disease (%)				0.368
Yes/no	29/71	35/65	13/87	
Last dental visit within one year (%)				0.623
Yes/no	43/57	41/59	25/75	
CPI (%)				
1	14	9	0	0.033
2	60	54	38	
3	21	28	25	
4	5	9	37	
Number of teeth (n)	23	24	26	0.157

CPI: Community Periodontal index, Periodontal attachment loss, bone loss and, ultimately, possible tooth loss, epi-bold number indicates statistical significance (p<0.05)

Stress, depression and anxiety are not yet confirmed as definite risk factors for periodontal disease but considered as potential risk factors in the concurrency and progression of periodontal disease (20,21). Boyce et al. (41) suggested that fear and anxiety continue to be the main reason patients avoid or do not follow up with dental care. Individuals with high dental anxiety would postpone dental treatments and delayed treatment might lead to more painful interventions and this experience might exacerbate the person's level of dental fear, this situation described as "vicious cycle" (42). Dental fear appears to play an important role in this cycle, not only affecting the likelihood that people will delay going to the dentist, also modifying the association between dental avoidance and subsequent treatment need (43). Patients attending a dental faculty were selected in the present study. However, subjects with high dental anxiety may not ask for dental treatment unless they had to, and this situation might be the cause of lower percentages of high dental anxiety in the present study. Subjects with higher CPI scores showed significantly higher dental anxiety compared to those of lower CPI scores in the present study. Our results were in accordance with the studies by Yildirim (4) and Talo Yıldırım et al. (24) reported that periodontal status was better in patients those had low and moderate dental fear scores compared to patients that had high dental fear scores. On the other side, Sezer et al. (25) and Ay et al. (23) have found no statistically significant difference on dental anxiety levels related to periodontal status. Conflicting results among studies may be explained by the fact that periodontal disease severity of the patients was different among studies (4,23-25). Periodontal disease is usually painless and chronic; therefore patients do not become sufficiently aware and anxious before it reaches a certain level (5,25). In order to determine whether periodontal disease severity really affect the level of dental anxiety, it is useful to conduct studies in different groups in terms of periodontal health status. A sample to fully represent the society may reveal different findings as it may involve individuals with both anxiety levels and different periodontal health levels. Our study has some limitations. Previous distressing experiences are often cited as the major factor in the development of dental anxiety (43,44). In the present study, previous negative dental experiences have not been evaluated. Further research including this topic is needed to clarify the role of previous dental experiences in the genesis of dental anxiety. The other limitation is the CPI index system. CPI index is based on a hierarchical concept of the progression of periodontitis, shows that a tooth with a score of 3 or 4 (a pocket present) should also have calculus present (score 2) and bleeding (score 1) (45-47). Also, it does not measure tooth mobility or attachment loss or furcation involvement (48,49). Additionally, full mouth assessments including existent/filled/decayed teeth of the patient provide more precise information about oral health (50). Therefore, further studies including whole oral assessment would help to evaluate the relationship between oral health and dental anxiety. Lastly, the present cross-sectional study has been conducted on a limited population who referred to a dental school in İzmir. The cross-sectional design might be insufficient to demonstrate whether dental anxiety worsens periodontal health or presence of periodontal disease causes dental anxiety. Also, subjects with high dental anxiety would not ask for dental treatment unless they had to, and this situation might have affected the number of subjects with dental phobia in the present study. Therefore, multicenter studies with larger populations are needed to reveal the prevalence and severity of dental anxiety in Turkish population.

Conclusion

The present study indicates that females and young people have higher dental anxiety than males and older people. Since younger people had higher dental anxiety, encouragement of these people for regular and more often dental visits would help to lower the dental anxiety. Also, within the limits of this study the results showed that severity of periodontal disease might be the result of dental anxiety and vice versa. In order to determine whether periodontal disease severity really affect the level of dental anxiety, it is useful to conduct studies in different groups in terms of periodontal health status.

Ethics

Ethics Committee Approval: Ethical Committee of Ege University Faculty of Medicine (approval no: 15-9.1/13).

Informed Consent: Written informed consent was obtained from all those wishing to participate in

accordance with Helsinki Declaration.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: G.E., Concept: G.E., Design: G.E., Data Collection or Processing: G.E., O.T., Analysis or Interpretation: O.T., Literature Search: O.T., Writing: G.E., O.T.

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Original Article / Özgün Araştırma

The Effects of Two Different Self-Adjusting File Working Times and Three Different Chelating Agents on the Root Canal Filling Bond Strength

İki Farklı Self-Adjusting File Çalışma Süresinin ve Üç Farklı Şelasyon Ajanının Kök Kanal Dolgusunun Bağlanma Dayanımı Üzerine Etkileri

Tuğrul Aslan, İbrahim Şener

Erciyes University Faculty of Dentistry, Department of Endodontics, Kayseri, Turkey

Keywords
Bonding, citric acid, ethylenediaminetetraacetic acid, root canal therapy, peracetic acid

Anahtar Kelimeler
Bağlanma, sitrik asit, etilendiamintetraasetik asit, kök kanal tedavisi, perasetik asit

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Address for Correspondence/Yazışma Adresi:
Tuğrul Aslan MD,
Erciyes University Faculty of Dentistry,
Department of Endodontics, Kayseri, Turkey
Phone : +90 506 810 76 88
E-mail : dr.tugrulaslan@hotmail.com
ORCID ID: orcid.org/0000-0002-5055-1551

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Abstract

Objective: The aim of this study was to investigate the effects of two different self-adjusting file (SAF) working times and three different chelating agents on the push-out bond strength of root canal fillings in oval root canals.

Materials and Methods: Eighty mandibular premolars were selected and distributed into 8 groups (n=10): 4 min SAF (G1), 4 min SAF + 17% ethylenediaminetetraacetic acid (EDTA) (G2), 4 min SAF + 10% citric acid (CA) (G3), 4 min SAF + 1% peracetic acid (PAA) (G4), 6 min SAF (G5), 6 min SAF + 17% EDTA (G6), 6 min SAF + 10% CA (G7), and 6 min SAF + 1% PAA (G8). The root canals were filled using gutta-percha and AH Plus root canal sealer, and the teeth were prepared for the push-out assessments using 1.0 mm thick root slices. Loading was performed with a universal testing machine at a speed of 0.5 mm/min; and then, collected data were analyzed statistically (α=0.05).

Results: While the different chelating agents significantly affected the push-out bond strength of the root canal filling ($p<0.05$), the different SAF working times did not ($p>0.05$). There were no significant differences among the groups in the apical and middle thirds of the roots ($p>0.05$). In the coronal thirds, G6 and G8 indicated significantly greater bond strength values than G1 and G5 ($p<0.05$).

Conclusion: According to the results, the 4 and 6 min SAF working times did not affect the bond strength of the root canal filling. PAA and EDTA can be recommended for root canal irrigation after SAF usage.

Öz

Amaç: Bu çalışmanın amacı, oval kök kanallarında iki farklı self-adjusting file (SAF) çalışma süresinin ve üç farklı şelasyon ajanının kök kanal dolgusunun push-out bağlanma dayanımı üzerine etkisinin araştırılmasıdır.

Gereç ve Yöntemler: Seksen adet mandibular premolar diş seçildi ve 8 gruba dağıtıldı (n=10): 4 dk SAF (G1), 4 dk SAF + %17'lik etilendiamintetraasetik asit (EDTA) (G2), 4 dk SAF + %10'luk sitrik asit (SA) (G3), 4 dk SAF + %1'lik perasetik asit (PAA) (G4), 6 dk SAF (G5), 6 dk SAF + %17'lik EDTA (G6), 6 dk SAF + %10'luk SA (G7), 6 dk SAF + %1'lik PAA (G8). Kök kanalları güta-perka ve AH Plus kanal patı kullanılarak dolduruldu ve dişler 1,0 mm kalınlıklı kök kesitleri kullanılarak push-

out incelemesi için hazırlandı. Yükleme işlemi bir üniversal test cihazı kullanılarak 0,5 mm/dk hızında gerçekleştirildi ve istatistiksel yorumlamalar yapıldı (α=0,05).
Bulgular: Farklı şelasyon ajanları kök kanal dolgusunun push-out bağlanma dayanımını anlamlı olarak etkilerken (p<0,05), farklı SAF çalışma süreleri etkilemedi (p>0,05). Köklerin apikal ve orta üçlülerinde gruplar arasında anlamlı farklılık yoktu (p>0,05). Koronal üçlülerde, G6 ve G8, G1 ve G5'ten anlamlı olarak daha yüksek bağlanma dayanımları gösterdi (p<0,05).
Sonuç: Bulgulara göre, 4 dk ve 6 dk SAF çalışma süreleri kök kanal dolgusunun bağlanma dayanımını etkilememiştir. SAF kullanımından sonra kök kanallarının irrigasyonu için PAA ve EDTA kullanılması önerilebilir.

Introduction

Probably the most important criteria for an ideal root canal therapy is the removal of microorganisms from the root canals (1). However, mechanical instrumentation alone cannot reduce the microbial population in the root canal system, since it creates a smear layer and debris on the dentinal wall surfaces (2). The smear layer and debris could hamper the close contact between the root canal filling material and the dentin (3). Therefore, irrigation solutions act a vital role in the chemomechanical preparation of root canals through the removal of inorganic and organic remnants and the smear layer (4). Moreover, the usage of chelating agents and organic material solvents, alone or in combination, is the fundamental method for smear layer removal (5).

Both rotary and reciprocating instruments touch less than 60% of the root canal wall surfaces due to the oval, flat, or irregular shaped canal morphologies (6,7). They also cause hard-tissue debris accumulation in the isthmus regions and the lingual and/or buccal recesses of the oval canals, preventing the removal of debris and jeopardizing the root filling quality (8). A self-adjusting file (SAF) instrument (ReDent Nova, Ra'anana, Israel) can adapt three-dimensionally to the root canal's morphology via its highly compressible structure (9). The SAF works in a way similar to sandpaper on the root canal walls because this instrument has no cutting edge flutes (10). It can be used with a VATEA irrigation device (ReDent Nova) that delivers irrigation continuously through the hollow file.

The goal of this *in vitro* investigation was to appraise the effects of two different SAF working times and three different chelating agents on the push-out bonding strength of root canal fillings in ovoid-shaped root canals.

The null hypotheses of this investigation were as follows:

1. Different SAF system working times and various chelating agents do not affect the bonding strength of the root canal filling.

2. The bonding strength of the root canal filling does not vary among the experimental groups in three different root regions.

Materials and Methods

This investigation was confirmed by the Local Ethics Committee of Erciyes University of Medical Sciences (approval number: 2017/449).

Eighty mandibular premolar human teeth of similar sizes and oval root morphologies, fully developed apices, and no previous endodontic treatment, and that were predominantly extracted due to periodontal diseases were chosen randomly for this research. The access cavity preparations were done by using a diamond fissure drill (Dentsply Maillefer, Ballaigues, Switzerland) in a handpiece at a high-speed under water cooling. For the working length determinations a 10 K-type hand file was placed inside the root canal till it could be detected at the apex, and 1 mm was subtracted from the measured length. Teeth were distributed into eight groups randomly (n=10):

Group 1 (G1): 4 min SAF usage with 5.25% sodium hypochlorite (NaOCl).

Group 2 (G2): 4 min SAF usage with 5.25% NaOCl, then 17% ethylenediaminetetraacetic acid (EDTA).

Group 3 (G3): 4 min SAF usage with 5.25% NaOCl, then 10% citric acid (CA).

Group 4 (G4): 4 min SAF usage with 5.25% NaOCl, then 1% peracetic acid (PAA).

Group 5 (G5): 6 min SAF usage with 5.25% NaOCl.

Group 6 (G6): 6 min SAF usage with 5.25% NaOCl, then 17% EDTA.

Group 7 (G7): 6 min SAF usage with 5.25% NaOCl, then 10% CA.

Group 8 (G8): 6 min SAF usage with 5.25% NaOCl, then 1% PAA.

All of the procedures were performed by one operator to standardize the experiments. In all groups, the SAF instrument was operated using a pecking motion in combination with a continuing flow of 5.25% NaOCl (0.4 mm amplitude and 5.000 vibrations per minute) supplied by the VATEA peristaltic motor at a flowing rate of 6 mL/min in the 4 min groups, and 4 mL/min in the 6 min groups. As a result, 24 mL of NaOCl was used in each group. All of the chelating agent irrigations were performed using the conventional syringe irrigation technique. A 30-gauge needle was introduced 1 mm short of the working length of the root canal, and 3 mL of 17% EDTA, 3 mL of 10% CA, or 3 mL of 1% PAA was delivered for 3 min in each specimen to remove the smear layer. Then finally, 3 mL of distilled water was used for 3 min for the rinsing of each specimen.

Absorbent paper points were used to dry the root canals. By using the cold lateral compaction technique, root canals were obturated with AH Plus root canal sealer (Dentsply DeTrey GmbH, Konstanz, Germany) and gutta-percha (DiaDent Group International, Chungcheongbuk-do, Korea). To confirm the completed fillings buccolingual and mesiodistal radiographs were obtained. The excess gutta-percha was cut from the cementoenamel junction level by using a heated hand plugger, and the access cavities were covered with Cavit G (3M ESPE, Seefeld, Germany) temporary filling material. Then, the teeth were kept at 37 °C in 100% humidity for 7 days for the fully setting of the root canal sealer.

All roots were cut perpendicularly to the long axis of the roots by using diamond-coated saw at a slow-speed (IsoMet; Buehler, Lake Bluff, IL, USA) to acquire three 1 mm thick specimens (one from the apical, one from the middle, and one from coronal third). A digital caliper was used to verify the 1 mm thickness of the specimens. Subsequently, all of the specimens were inspected with an operating microscope (OPMI pico; Zeiss, Germany) to determine if any artifacts or cracks occurred as a result of the slicing process, and no artifacts or cracks were seen. A felt tip marker was used to define the apical sides of each specimen. Next, a cylindrical plunger which was made of stainless steel (diameter of 0.5, 0.7, or 0.8 mm for the apical, middle, and coronal regions, respectively) was selected and located to cover the majority of the root filling surface as possible upon loading, while refraining any touch with the canal walls. The root canal fillings were subjected to the loads from the apical to the coronal direction. Push-out bond strength tests were done with a universal testing machine (Instron, Canton, MA, USA) at a cross-head speed of 0.5 mm/min until dislodgement happened (Figure 1). The force required to dislodge the root filling was saved in Newtons (N). Then, the dislodgement force was converted to shear stress (in MPa) by dividing the dislodgement force by the surface area of the bonded interface of a trapezoid, as Pereira et al. (11) used in their study. The surface area was calculated by taking the average of the length of the perimeter of the root filling in millimeters on the apical and coronal sides of each specimen and multiplying it by the height of the slice.

To assess the failure modes of loaded slices, an operating microscope was used at 10x magnification. Failure modes were evaluated according to three categories: adhesive failure (no root canal sealer on the dentin surface), cohesive failure (surface of the dentin was covered with sealer), and mixed failure (cohesive and adhesive failure modes mixture).

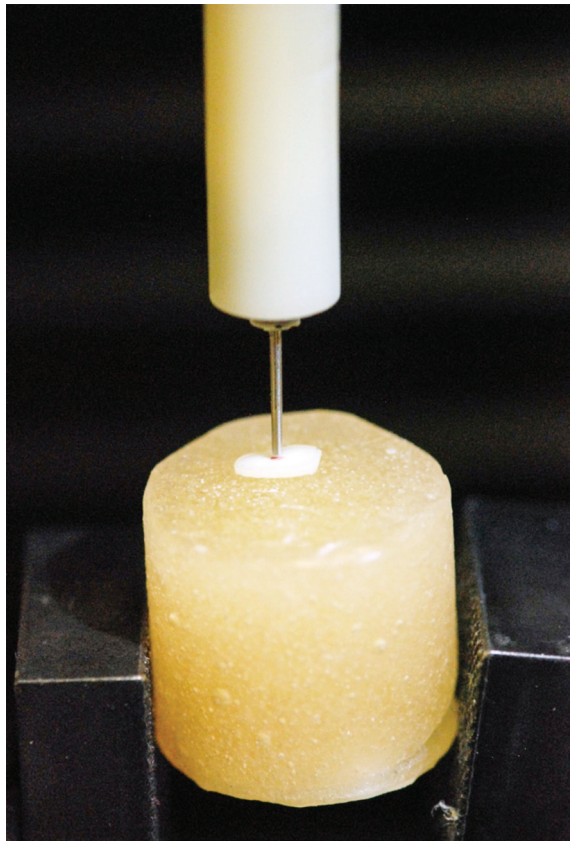

Figure 1. Loading the specimens in a universal testing machine

Statistical Analysis

The collected data were assessed statistically by using a Two-Way ANOVA test (chelating agent and working time) with SPSS software (SPSS 20.0; SPSS Inc., Chicago, IL, USA). To make pairwise comparisons among the groups, The One-Way ANOVA and Tukey's post-hoc tests were used (α=0.05). The failure modes of the groups were expressed as frequencies.

Results

Two-Way ANOVA test showed that while the different chelating agents significantly affected the push-out bonding strength of the root canal filling ($p<0.05$), the different SAF working times did not ($p>0.05$) (Table 1). No significant differences detected among the groups in the apical and middle thirds of the roots ($p>0.05$). Moreover, in the coronal third, G6 and G8 showed greater bonding strengths than G1 and G5 ($p<0.05$) (Table 2). The error bar graph of the bonding strength values is shown in Figure 2.

While the cohesive and mixed failures were observed the most frequently in all of the groups; adhesive failure mode was the least observed. Distributions of failure modes are shown in Table 3 according to the root thirds.

Discussion

Oval-shaped root canals represent a major challenge to prepare and fill (12); therefore, mandibular premolar teeth with oval root canal morphology were selected for the present study. SAF instrument was manufactured to cope with the mismatch problem of nickel titanium (NiTi) rotary files with the irregular shape of the root canal system (9). The irrigation solution passing through the instrument's oscillating metal lattice enhances the efficiency of debridement of the root canal (13). Paque et al. (14) showed that the SAF system preparation produced less hard-tissue debris during instrumentation than the traditional NiTi rotary preparation.

NaOCl is one of the most common used irrigation solutions in root canal treatment (15). It has a strong antimicrobial effect and is able to dissolve necrotic and organic tissues; however, it is not capable of dissolving the inorganic components of the smear layer (16). The inorganic part of the smear layer can be removed by chelating agents; thus, exposing a great number of dentin tubules, which may enhance adhesion due to the increased contact area and improve the adaptation between the root canal sealer and the dentin (3). Hence, the consecutive use of inorganic and organic solvents as irrigation solutions has been suggested, because there has been no proven single irrigation solution that can remove the smear layer

Table 1. Two-Way ANOVA test results

Factors	Sum of squares	Mean square	F	Significantly
Working time	1.40	1.40	1.31	0.25
Chelating agent	24.86	8.28	7.77	0.00

Table 2. Means and standard deviations of the groups according to the root thirds

Root thirds	Groups	Mean (MPa)	Standard deviation
	4 min. SAF^{a}	1.92	0.38
	4 min. SAF + EDTA^{a}	1.98	0.56
	4 min. SAF + CA^{a}	1.97	0.66
Apical	**4 min. SAF + PAA^{a}**	2.49	0.70
	6 min. SAF^{a}	2.04	0.44
	6 min. SAF + EDTA^{a}	2.26	0.55
	6 min. SAF + CA^{a}	2.00	0.40
	6 min. SAF + PAA^{a}	2.52	0.58
	4 min. SAF^{b}	2.70	0.73
	4 min. SAF + EDTA^{b}	3.46	0.86
	4 min. SAF + CA^{b}	3.39	1.09
Middle	**4 min. SAF + PAA^{b}**	3.70	0.83
	6 min. SAF^{b}	2.84	0.59
	6 min. SAF + EDTA^{b}	3.62	0.89
	6 min. SAF + CA^{b}	3.55	0.64
	6 min. SAF + PAA^{b}	3.75	0.82
	4 min. SAF^{c}	2.98	0.76
	4 min. SAF + EDTA^{c}	3.96	0.96
	4 min. SAF + CA^{c}	3.83	0.60
Coronal	**4 min. SAF + PAA^{c}**	4.20	0.78
	6 min. SAF^{c}	3.05	0.68
	6 min. SAF + EDTA^{d}	4.29	0.83
	6 min. SAF + CA^{c}	3.91	1.05
	6 min. SAF + PAA^{d}	4.44	0.81

*Significantly different groups are shown with different superscript letters, SAF: Self-adjusting file, PAA: Peracetic acid, EDTA: Ethylenediaminetetraacetic acid, CA: Citric acid, MPa: Marine protected area

alone yet (17). In this study, three different chelating agents were used after the SAF instrumentation in combination with the NaOCl. In all of the groups, in total, 24 mL of NaOCl was used to standardize the irrigation volume.

Even in the presence of organic matter PAA is not inactivated, does not leave residue, and does not produce environmentally harmful byproducts (18,19). Moreover, investigations into its use in endodontics have revealed its ability to remove the smear layer (19,20). Another chelating solution, EDTA, is a widely used and effective chelating agent that can dissolve the mineralized part of the smear layer (3,21). For effectively removing of the smear layer from the dentinal walls a combination of EDTA and NaOCl is suggested (22). One previous study reported that operating the SAF system in combination with EDTA and NaOCl irrigation provided a root canal wall that was significantly free of the smear layer (13). Furthermore, CA is a weak organic acid that is used as an aqueous acidic solution (23). In the literature, there are some studies that compare the smear layer removal effectiveness of EDTA and CA; however, those findings are contradictory. Certain studies reported that 10% CA is more effective than EDTA (24,25); in contrast, some studies found no significant difference between them (23,26).

In the present study, the root canal filling was applied using gutta-percha and AH Plus epoxy resin based sealer with a lateral compaction method, which is the most commonly used root canal filling technique in clinical practice. AH Plus binds with the organic phase of dentin, and the binding of the root canal sealer to the root dentin sustains the integrity of the sealer-dentin interface over the long term (27,28).

The manufacturer of the SAF system advises a 4 min use of the instrument under constant irrigation solution flow (29). In addition, studies using the SAF system at different working times are available in the literature. These studies are about the amount of deformation of the SAF instrument and the reduction of the number of microorganisms in the root canal (30,31). However, there are no studies in the literature about the effects of various SAF working times on the

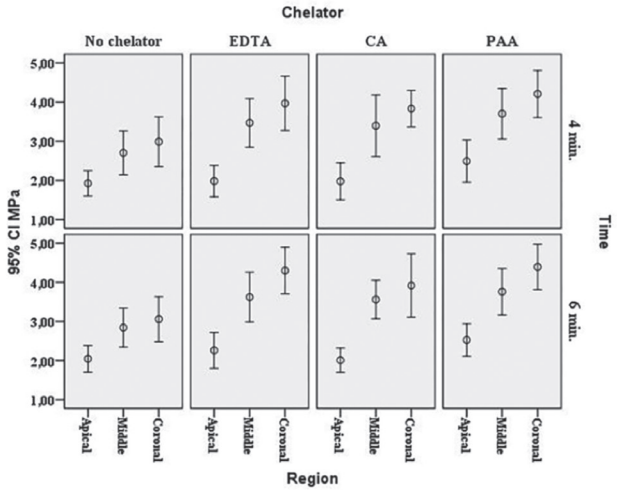

Figure 2. Error bar graph of the tested groups
EDTA: Ethylenediaminetetraacetic acid, CA: Citric acid, PAA: Peracetic acid, CI: Confidence interval, MPa: Marine protected area

Table 3. Failure mode distributions of the groups according to the root thirds

Groups	Root thirds	Adhesive	Cohesive	Mix
4 min. SAF	Apical	2	4	4
	Middle	0	4	6
	Coronal	1	4	5
4 min. SAF + EDTA	Apical	2	5	3
	Middle	1	7	2
	Coronal	0	5	5
4 min. SAF + CA	Apical	3	4	3
	Middle	1	5	4
	Coronal	0	4	6
4 min. SAF + PAA	Apical	2	3	5
	Middle	2	4	4
	Coronal	0	4	6
6 min. SAF	Apical	3	3	4
	Middle	1	4	5
	Coronal	1	3	6
6 min. SAF + EDTA	Apical	2	5	3
	Middle	2	4	4
	Coronal	0	6	4
6 min. SAF + CA	Apical	2	3	5
	Middle	0	2	8
	Coronal	0	3	7
6 min. SAF + PAA	Apical	1	3	6
	Middle	1	3	6
	Coronal	1	4	5

SAF: Self-adjusting file, PAA: Peracetic acid,
EDTA: Ethylenediaminetetraacetic acid, CA: Citric acid

push-out bonding strength of the root filling to the dentinal walls. In our results, the Two-Way ANOVA test showed that the different SAF working times did not affect the results ($p>0.05$). Hof et al. (10) stated that major abrading effectiveness of the instrument and most of the root canal shaping occurred at first 2 min of usage. However, SAF instruments can be worn out after such a prolonged use; therefore, this result is not surprising. There might not have been much greater canal preparation among the experimental groups, and this might not have made a difference in terms of the working time.

According to the findings of this study, no significant difference was observed among the groups in the apical thirds ($p>0.05$). This could be because a lower amount of irrigant reached the apical area and sclerotic structure of the dentinal tubules in the apical region. In addition, the more complex structure of the dentinal tubules in the apical area can make the penetration of epoxy resin into the tubules difficult (27). There were no significant differences among the experimental groups in the middle thirds ($p>0.05$), which could be due to the flushing of the middle regions with a higher amount of irrigating solution. Lastly, in the coronal thirds, no significant differences were observed among the groups ($p<0.05$). G6 and G8 showed significantly greater bonding strengths than G1 and G5 ($p<0.05$). In addition, the Two-Way ANOVA test showed that the chelating agent type affected the bond strength values ($p<0.05$), suggesting that the use of EDTA and PAA after the 6 min SAF system preparation enhanced the bond strength of the root canal filling in the coronal third. This could be the result of a longer NaOCl agitation time in the coronal third, which has a greater canal space that can fill up with irrigant. Following the chelator, application with PAA and EDTA might cause cleaner dentinal walls and greater bond strengths than in the no chelating agent groups. In one previous study, the authors indicated that exposure of the organic phase with EDTA was significant for the ability of the AH Plus root canal sealer to adhere to the root dentin (27). In addition, De-Deus et al. (20) stated that PAA is as effective as a 17% EDTA solution in terms of dissolving the smear layer.

In all of the groups, the least observed failure mode was adhesive failure. This finding may indicate relatively clean dentinal walls due to the effective debridement capability of the SAF system, and thus, the enhanced binding of the root canal sealer to the dentin surface. Higher frequencies of the cohesive and mixed failure types in the groups could be attributed to the mismatch of the cylindrical form of the plungers used and the oval shape of the root canals. Therefore, the root canal filling may have been left in the recesses of the canal.

Conclusion

The bonding strength of the root canal filling was not affected by the 4 min vs. 6 min SAF working times. Furthermore, the use of PAA and EDTA can be recommended for irrigating the root canals after SAF system usage. However, there is a need for further studies to investigate the activities of varied irrigation solutions during or after the use of SAF over different periods of time.

Ethics

Ethics Committee Approval: This investigation was confirmed by the Local Ethics Committee of Erciyes University of Medical Sciences (approval number: 2017/449).

Informed Consent: Written consent wasn't obtained because operation was made on extracted teeth.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: T.A., İ.Ş., Design: T.A. Data Collection or Processing: İ.Ş., Analysis or Interpretation: T.A., Literature Search: T.A., İ.Ş., Writing: T.A.

Conflict of Interest: No conflict of interest was declared by the authors.

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Original Article / Özgün Araştırma

Evaluation of the Internal Accuracy of Molar Crowns Fabricated Using Digital and Conventional Impression Techniques

Dijital ve Geleneksel Ölçü Yöntemi ile Hazırlanan Molar Kronların İnternal Doğruluklarının Değerlendirilmesi

Bülent Kadir Tartuk, Emrah Ayna, Emine Göncü Başaran

Dicle University Faculty of Dentistry, Department of Prosthodontics, Diyarbakır, Turkey

Keywords
Intraoral scanner, digital impression, internal fit

Anahtar Kelimeler
Ağız içi tarayıcı, dijital ölçü, internal uyum

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Address for Correspondence/Yazışma Adresi:
Bülent Kadir Tartuk MD,
Dicle University Faculty of Dentistry,
Department of Prosthodontics, Diyarbakır,
Turkey
Phone : +90 507 047 21 39
E-mail : kadirtartuk@gmail.com
ORCID ID: orcid.org/0000-0003-2282-8944

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Abstract

Objective: The purpose of this *in vitro* study was to compare the internal gaps of 3 different full molar crowns prepared using digital and conventional impression techniques.

Materials and Methods: A zirconia model with a prepared maxillary first molar was used as the base model. Sixty crown restorations were produced using zirconia, polyether ether ketone and hybrid ceramic from the same datasets. The specimens divided into 2 groups that were fabricated as follows: for the group conventional impression (CZ; CP; CH, n=10), vinyl siloxane ether impressions of the master model were made. For the group digital impression (DZ; DP; DH, n=10), digital impressions of the master model using intraoral scanner system were made. The internal accuracy of the frameworks were measured under a reflected stereo microscope by using the silicon replica technique. ANOVA and the Tukey-HSD multiple comparison tests were used.

Results: There was no significant statistical difference between the conventional and digital impression techniques in relation to the internal fit ($p>0.05$). Group DH (81.74 µm) showed the lowest values for internal fit, while group CZ (102.2 µm) showed the largest.

Conclusion: Within the limitations of this *in vitro* study, it was concluded that the marginal fit produced by the digital and conventional impression techniques showed the same values, and all the samples were measured at a clinically acceptable internal fit (<200 µm).

Öz

Amaç: Bu *in vitro* çalışmanın amacı, dijital ve geleneksel ölçü yöntemi ile üretilen 3 farklı molar kronların internal aralıklarının hesaplanıp değerlerin karşılaştırılmasıdır.

Gereç ve Yöntemler: Maksiller birinci molar olacak şekilde zirkonyum ana model olarak kullanıldı. Materyaller zirkonyum, polieter eter keton ve hibrit seramik olarak belirlendi, ana modelden 60 adet molar kron üretildi. Kron üretimi esnasında aynı veriler kullanıldı. Denekler 2 ana gruba ayrıldı: Geleneksel ölçü yöntemi için vinil Siloksan eter ölçü materyali kullanıldı (CZ; CP; CH, n=10). Dijital ölçü yöntemi için ise ağız içi tarayıcı sistemi kullanıldı (DZ; DP; DH, n=10). Elde edilen bütün kronların

internal aralık değerlerinin hesaplanması için silikon replika tekniği kullanıldı. Gruplar arası istatistiksel farkları saptamak için ANOVA ve Tukey-HSD çoklu karşılaştırma testi kullanıldı.

Bulgular: Dijital ve geleneksel ölçü yöntemleri istatistiksel olarak karşılaştırıldıklarında anlamlı fark gözlenmedi (p>0,05). En düşük internal aralık değer ortalaması DH (81,74 µm) grubunda gözlenirken, en yüksek değer CZ (102,2 µm) grubunda gözlendi.

Sonuç: Sunmuş olduğumuz *in vitro* çalışma doğrultusunda dijital ölçü yöntemi ile üretilen kronların ile geleneksel ölçü yöntemi ile üretilen kronların internal uyumları arasında fark gözlenmedi (p>0,05). Dijital ve geleneksel ölçü yöntemi ile üretilen bütün örneklerin internal aralık değerleri klinik olarak kabul edilebilir aralık değerinde ölçüldü (<200 µm).

Introduction

Dental treatment is moving toward digital technology (1). For 30 years, computer-aided design and computer-aided manufacturing (CAD/CAM) has been used to fabricate fixed dental prostheses (FDPs) in digital dentistry (2). Today, many framework materials for FDPs are fabricated using CAD/CAM technology, such as zirconia, high-resistance polymers (polyether ether ketone), and hybrid ceramic restorations, which use mechanical properties and biocompatibility to provide sufficient mechanical resistance to chemical attacks and to determine clinical success (3-6).

Internal adaptation is a key factor in the clinical success of dental restorations (7). The precision of the details is critical in terms of model accuracy, and the internal fit influences preconditions for the clinical performance of the indirect restorations (8-12). When referring to the fit between the teeth and the restoration, the existing restoration is referenced as the internal fit. Poor internal fit of indirect restorations can cause distribution of the microflora and can increases plaque retention (13), which can lead to the occurrence of secondary caries, microleakage, pulpitis, and periodontal diseases (13-16). It also will weaken the fracture strength and mechanical properties of the restorations (9,17,18).

The type of impression material and impression technique used will affect the internal fit of a prosthetic restoration. The conventional impression technique is used as a standard in prosthetic dentistry, owing to its ease of application, adequate stability and precision, low cost, and the short time required to perform the procedure (19,20). However, this technique relies upon impression materials and master dies, so the potential for distortion of the impression material exists (21-23). Deformation and errors caused by impression materials (such as expansion or shrinkage) will affect the accuracy of the master die and can jeopardize the fit of the FDP (24).

Christensen (25) emphasized that more than 50% of measurements obtained by the conventional impression technique cannot be used to determine an acceptable internal fit due to errors caused by the impression materials. In addition, prostheses produced from an unclear impression recording are not compatible with dental tissue (25).

Researchers have worked to improve the process of creating impression materials by seeking out a more accurate method for dental impressions. Therefore, the digital impression technique was developed to address this need by increasing the accuracy of the definitive FDP while simplifying the process (26).

The advantage of digital impressions is that they involve faster lab processing than conventional impressions, the data can be stored indefinitely, and the images can be transmitted digitally (27). In addition, the digital impression technique increases patient comfort, reduces errors caused by impression materials, provides three-dimensional visual analysis between physicians and patients, and generates higher profits by reducing costs associated with the creation of dental prosthetics (28). Despite these advantages, the digital impression technique cannot provide a clear bit recording in the subgingival region and can cause a reduced sensitivity to blood and saliva (29,30). Previous studies have evaluated the precision of an intraoral scanner and have revealed that similar or more accurate results could be achieved compared to those produced by conventional vinyl siloxane ether or silicon impression materials (13,14), while other studies have reported that scanners are less accurate than conventional impressions (22). As a result, there is no consensus about which impression technique is better in terms of internal accuracy (31).

The purpose of this study was to compare and evaluate the internal adaptation of framework fabrication using two impression techniques, and it was hypothesized that there would be no difference

in the clinical internal fit of framework when either an intraoral scanner or a vinyl siloxane ether impression material has been utilized to develop an impression technique.

Materials and Methods

In the present study, a zirconia base model (Zirconia Pre Shaded Blank; Shenzhen Upcera Co, Shenzhen, Yuè, China) with a prepared maxillary first molar, which included a minimum occlusal reduction of 2.0 mm, an axial reduction of 1.5 mm and a chamfer with convergence angle of 6 °C (Figure 1).

In this model, crowns were produced using the digital and conventional impression technique and 3 different materials. The materials were fabricated from zirconia, high resistance polymer (PEEK Optima LT1, In vivo Biomaterial Solutions Inc, Lancashire, England), and hybrid ceramics (Cerasmart; GC America Inc, Alsip, IL, USA). A total of 10 crowns were preferred for each group. In total, 60 molar full crowns were produced using the CAD/CAM system machine (Yena D15; Turkuaz Inc, İzmir, Turkey). The ethics committee approval was not necessary since the study was *in vitro*.

Conventional Impression Technique

First, conventional impression with a vinyl siloxane ether (GC Exa'lance; GC America Inc, Alsip, IL, USA) of the zirconia model were made using custom trays. According to the manufacturer, the impression material requires 6 min to set fully. Due to the controlled room temperature of this study, the setting time was extended for about 2 min to a total time of 8 min. Twenty-four hours later, The master cast was fabricated with a type I4 stone (Fujirock; GC America Inc, Alsip, IL, USA). The stone cast was scanned with a model scanner (Dental Wings 7 Series; Dental Wings Inc, Montréal, QC, Canada) and all data were transferred and saved as an stereolithography (STL) file. Subsequently, each CAD process STL file was sent and the design of the 30 frameworks was performed:

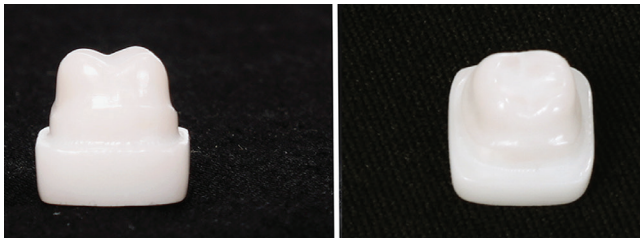

Figure 1. Photograph of a zirconium model

10 frameworks were produced from polyether ether ketone (CP), 10 frameworks were produced from zirconia (CZ), and 10 frameworks were produced from hybrid ceramic (CH).

The complete the design of the frameworks required the use of a 3-axis milling machine. Zirconia frameworks were sintered at a temperature of 1500 °C to full density in a sintering furnace (Lava Furnace 200; 3M ESPE, St. Paul, MN, USA). However, only surface polishing processes were applied to the PEEK and Cerasmart frameworks without any sintering process.

Digital Impression Technique

The zirconia base model was scanned using the CEREC 3 intraoral scanner (Cerec Omnicam; Sirona Dental Systems Inc. NY, USA). According to the manufacturer, no powder system was needed on the zirconia model before scanning. The same parameters were used for both impression techniques during production. Thus, the aim was to produce the frameworks to the same standards for the 3 different materials obtained by both impression techniques, and all the frameworks were produced using the same CAM device.

The silicon replica technique was applied for measurement values of the internal gaps of the frameworks, which were filled with extra-light body silicon (yellow color) and were placed onto zirconia base model with a dynamometer pressure of 30 N. The frameworks were removed from the base model with extra-light body silicon. Then light body silicon (pink color) was also mixed to fill circumferentially the inside of thin extra-light body silicone of each crown. The replica specimen was removed from the frameworks, after setting the light body silicon had set. The replicas were sectioned with a razor blade throughout the mesio-distal directions (Figure 2).

Ten different points (four marginal, four axial, two occlusal) were evaluated on the mesio-distal sections of each specimen (Figure 3). All points were measured three times by the same operator, and the mean values for each point were recorded. When measuring the internal gap, reference points were chosen, as described by Martins et al. (11). In total, 600 measurements were performed on the 60 frameworks.

Statistical Analysis

The replicas were examined at ×40 magnification under a reflected stereo microscope (Olympus Dp25;

Olympus Corporation, Tokyo, Japan). The distances in the designated regions were calculated using the computer software (Adobe Photoshop CS; Adobe Systems Inc. San Jose, CA, USA), and the internal gap values were recorded in terms of micrometers (Figure 4).

All measurements were presented descriptively by means, standard deviation (SD) and the corresponding 95% confidence intervals (95% CI). Kolmogorov-Smirnov test was applied to test the data on the normal distribution within the groups. One-Way ANOVA test was used to compare the mean values, and the Tukey-HSD multiple comparison tests were used to determine how the material differed with regard to statistical significance.

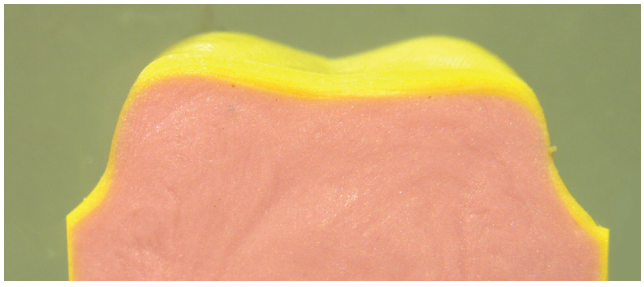

Figure 2. Image of the silicon replica

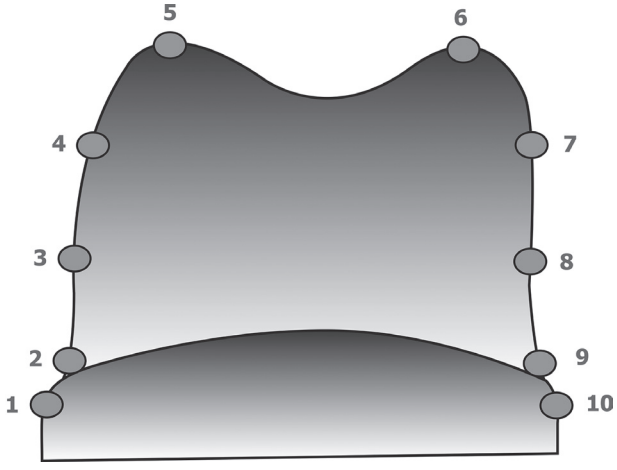

Figure 3. Mesio-distal section showing the locations of the measuring points

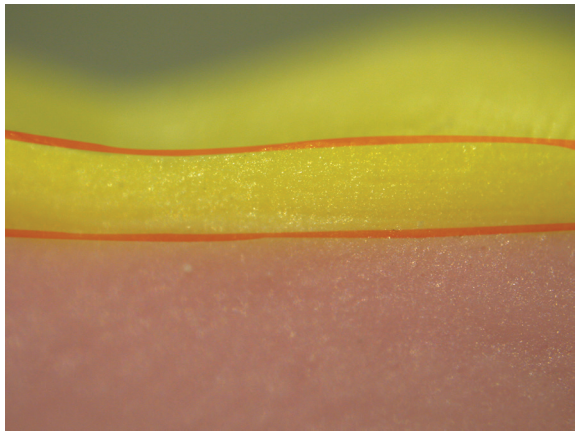

Figure 4. Lines drawn (in red) on the inner and outer surface of the low viscosity silicone

Results

The internal range average, minimum and maximum values, SDs, and standard errors for each group are shown in Table 1. The values obtained by the impression techniques were statistically compared using the One-Way ANOVA and Tukey-HSD multiple comparison tests (Table 2).

Within one framework material, different impression techniques showed in different distances between the manufactured frameworks and the zirconia model. For all groups, the minimum mean values were 0 µm, and the maximum mean values were 120 µm (Figure 5).

The zirconia group (CZ) revealed the highest mean value (102.22 µm) for the internal gap, while the lowest mean value (81.74 µm) of the internal gap was observed in the hybrid ceramic group (DP) (Figure 5). However, there was no significant differences in internal discrepancy were found between the digital impression group and digital impression group for the all materials ($p>0.05$) (Table 2).

Discussion

The purpose of the present study was to compare the internal fit of frameworks fabricated with conventional and digital impression techniques. The null hypothesis was accepted, as no differences would be found in internal fits among the frameworks fabricated with the both techniques.

In this study, based on the benefit of noninvasive and nondestructive method of the silicon replica technique, which has been reported to yield discrepancy measurements comparable with those of conventional cementation, was preferred (13,14,17). Several techniques can be used with the silicone replica technique for internal gaps measurement. Ueda et al. (14) used light microscopy to determine the internal gaps. Colpani et al. (10) compared the weight of silicone replicas to evaluate the adaptation

Table 1. Mean and range values for internal gaps

Material	Impression method	Mean (µm)	SD (µm)	SE (µm)	Min (µm)	Max (µm)
Zirconia	Digital (DZ)	98.6585	7.13704	2.25693	50.05	190.47
	Conventional (CZ)	102.2225	13.53664	4.28066	57.41	190.34
Hybrid ceramic	Digital (DH)	81.7415	12.20410	3.85927	55.33	187.3
	Conventional (CH)	93.6205	13.50449	4.27049	57.5	194.21
PEEK	Digital (DP)	93.6775	14.85664	4.69808	45.3	197.42
	Conventional (CP)	92.0300	8.85732	4.69808	62.57	195.27

SD: Standard deviation, Min: Minimum, Max: Maximum, SE: Standard error

Table 2. Multiple comparison of internal gaps with real p values for all groups with ANOVA analysis

Material	p	Mean difference	Standard error difference	95% CI difference	
				Lower bound	Upper bound
Zirconia	0.471	-3.56	4.83	-13.73	6.6
Hybrid ceramic	0.054	-11.87	5.75	-23.97	0.21
PEEK	0,767	1.64	5.46	-9.84	13.1

CI: Confidence intervals

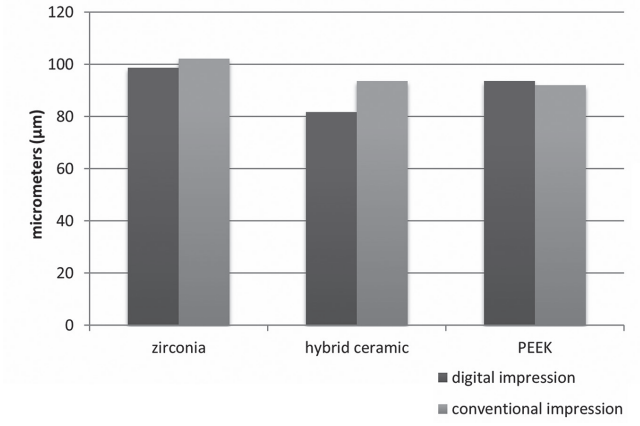

Figure 5. Bar graph of the measured mean values of frameworks

of indirect restorations. They showed that evaluating the internal gaps could be done by comparing the weights of the replicas.

In this study, the internal gap values of the PEEK and hybrid ceramic groups are similar, although the zirconia groups were found to have higher values. It is believed that the semi-sintered zirconia used in this study is due to the dimensional change in the sintering process which is characterized by a high sintering shrinkage, of circa of 20-30% that must be compensated in the milling procedure (15).

Ueda et al. (14) concluded that this procedure might negatively influence the final dimension of the restoration, and this present study found the same result for zirconia groups. On the other hand, PEEK and hybrid frameworks are milled without a sintering process. Yildiz et al. (15) evaluated the internal and fit of the zirconia frameworks fabricated with the digital impressions and the conventional impressions, and they pointed out that the increase in the internal and marginal gap values of the obtained crowns may be due to the dimensional change after the sintering.

This *in vitro* study revealed a mean internal gap of 95.95 µm for the conventional digital impression groups and 91.35 µm for the digital impression groups. Although both groups have shown clinically acceptable values for internal fit, the better overall fit of the digital impression group could be explained by error caused by the procedure of conventional impression technique. In which, stone casts were produced from impressions made from the original zirconia model. However, no significant differences were found between frameworks fabricated with both impression techniques.

For all the groups, the highest values for the internal gaps were calculated in the occlusal region, while the lowest values of internal gaps were calculated in the margin and axial region. According to published literature, the occlusal surface seems to be affected by factors that can be speculated as being problems related to the accuracy of the optical images acquired, which are not consistently reliable (11,12,15). Kokubo et al. (12) have reported that the scanner sensitivity of the CAD/CAM system affects the internal fit of the

restoration that is achieved. They reported that the internal gaps of the crowns produced by the CAD/CAM system are largest in the occlusal region and smallest in the proximal and marginal regions.

Theoretically, the internal gap necessary for the cement is 20-40 µm; however, in the clinical condition, this range is very rare (14). Some researchers have proposed that clinically acceptable value for maximum internal discrepancy ranging between 200 µm and 300 µm is also appropriate (16-18). In this study, although the internal gaps' values were designed to be 30 µm, the values obtained were calculated at the upper limit. However, the calculated internal gaps values were calculated below the clinically acceptable values determined in previous studies (12-14).

Ueda et al. (14) evaluated the marginal gaps of zirconia frameworks fabricated with using conventional impressions of the fit after making digital impressions. They showed no significant differences between the crowns produced by means of the conventional impression technique (mean, 141 µm) and the digital impression technique (mean, 121 µm). A recent report by Almeida e Silva et al. (23) investigated the internal fit of the zirconia frameworks produced on the basis of conventional impressions technique and digital impressions technique and no significant differences were seen between the impression techniques.

Syrek et al. (13) compared the accuracy of the impression techniques, and the digital impression technique showed a significantly better internal accuracy than the conventional impression technique. The digital impressions mean was 49 µm, and the conventional impressions mean was 71 µm ($p<0.05$). Ender and Mehl (22) reported that the conventional impression technique is more accurate and reliable than the digital impression technique in their study.

The digital impression technique and the conventional impression technique performed similarly in the CAD/CAM. However, the digital impression technique has been demonstrated to be preferable as an alternative to the conventional impression technique because of its short-time workflow, economy gains, and improvement in patient comfort.

Conclusion

Within the scope of this *in vitro* study, the following conclusions were drawn; the internal fit of the crowns produced by the conventional and digital impressions method showed no statistically significant difference for each materials. All groups fabricated using digital impression technique and conventional impression technique showed a clinically acceptable internal fit. Additionally, in all the groups, the internal gaps were the smallest in the axial area, whereas the occlusal areas of the internal gaps were the largest. However, the results of this study might not reflect the reality of in clinic conditions. The results we obtained for all these should be supported by in vivo studies. Moreover, this study evaluated only 1 type of prosthesis. Studies assessing partial FDP fabricated from digital and conventional impressions should be conducted.

Ethics

Ethics Committee Approval: The ethics committee approval was not necessary since the study was *in vitro*.

Informed Consent: For this type of study, formal consent is not required.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: B.K.T., E.A., E.G.B., Concept: B.K.T., E.G.B., Design: B.K.T., E.G.B., Data Collection or Processing: B.K.T., E.A., E.G.B., Analysis or Interpretation: B.K.T., E.A., E.G.B., Literature Search: B.K.T. E.A., Writing: B.K.T., E.G.B.

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Original Article / Özgün Araştırma

Parafunctional Habits and Their Relationship with Temporomandibular Joint Disorders in Iranian School Students

İranlı Öğrencilerin Parafonksiyonel Alışkanlıkları ve Temporomandibuler Eklem Hastalıklarıyla Olan İlişkileri

Maryam Alsadat Hashemipour[1,2,3], Fatemeh Moslemi[4], Azin Mirzadeh[5], Amir Mirzadeh[5]

[1]Kerman University of Medical Sciences, Member of Kerman Social Determinants on Oral Health Research Center, Kerman, Iran
[2]Kerman University of Medical Sciences, Kerman Dental and Oral Diseases Research Center, Kerman, Iran
[3]Kerman University of Medical Sciences, Department of Oral Medicine, Dental School, Kerman, Iran
[4]Kerman University of Medical Sciences, Department of Pediatric Dentistry, Dental School, Kerman, Iran
[5]Kerman University of Medical Sciences, Department of Oral Medicine, Dental School, Kerman, Iran

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Anahtar Kelimeler
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Address for Correspondence/Yazışma Adresi:
Maryam Alsadat Hashemipour MD,
Member of Kerman Social Determinants on Oral Health Research Center Clinic of Oral Medicine, Kerman, İran
E-mail : m.s.hashemipour@gmail.com

ORCID ID: orcid.org/0000-0002-4515-8974

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Abstract

Objective: Unfavorable parafunctional habits affect the dentoalveolar structures and if they are diagnosed late and if the treatment is delayed, they will lead to severe problems that are either irreversible or are associated with high costs, difficult technical problems and severe patient suffering. The aim of this study was to determine the prevalence of parafunctional habits and their relationship with temporomandibular joint (TMJ) disorders in female high school students in Kerman, İran.

Materials and Methods: In the present descriptive-analytical study, data were collected by completing a questionnaire and through clinical examination. The study population consisted of first- to fourth-grade high school students in Kerman, İran. Clinical examinations were carried out by one last-year dental student who was instructed in the faculty of dentistry in the relevant field by one professor and became proficient in clinical examination. Statistical analyses were carried out with SPSS 13.5, using t-test, chi-squared test and ANOVA.

Results: A total of 368 questionnaires were completed in this study. Sixty-six students had no parafunctional habits and 78% of the subjects had at least one oral parafunctional habit; 1.2% of the subjects had all the eleven parafunctional habits and 22% of the subjects had only one parafunctional habit. The highest frequencies were related to chewing gums on one side, sleeping on one side and chewing pencils or pens. The prevalence of TMJ disorder symptoms and signs in the subjects was as follows: joint clicks (31%), pain in masticatory muscles (10%), pain during mastication of food (24%) and pain at mouth opening (14%). The results showed the greatest relationship between tooth clenching and tenderness to palpation in masticatory muscles. Of all the masticatory muscles, the most severe pain during palpation was detected in the masseter, followed by temporalis muscle.

Conclusion: This study showed that the highest frequency of parafunctional habits was related to chewing gums and the most frequent sign of TMJ disorders was joint clicks in subjects. In addition, there were significant relationships between TMJ disorder symptoms and signs and parafunctional habits such as bruxism, unilateral mastication and tooth clenching.

Öz

Amaç: İstenmeyen parafonksiyonel alışkanlıklar dentoalveoler yapıları etkiler ve eğer geç tanı konurlarsa ve tedavi gecikirse, ya geri döndürülemez ya da yüksek masraf, zorlu teknik problemler ve ciddi hasta çekimi ile ilişkili ciddi problemlere neden olurlar. Bu çalışmanın amacı, İran'da Kerman'daki lise öğrencilerinin parafonksiyonel alışkanlık prevalansını ve temporomandibular eklem (TME) hastalıklarıyla olan ilişkilerini belirlemektir.

Gereç ve Yöntemler: Mevcut betimsel-analitik çalışmada, anket doldurularak ve klinik muayene ile veriler toplandı. Çalışma grubu, İran'ın Kerman kentinde bulunan lise son sınıf öğrencilerinden dördüncü sınıf öğrencilerinden oluşmaktadır. Klinik muayene, bir profesör tarafından ilgili alanda diş hekimliği fakültesinde eğitim görmüş ve klinik muayeneye hakim bir önceki yıl diş hekimliği öğrencisi tarafından gerçekleştirilmiştir. İstatistiksel analizler SPSS 13.5 ile t-testi, ki-kare testi ve ANOVA kullanılarak gerçekleştirildi.

Bulgular: Bu çalışmada toplam 368 anket doldurulduu. Altmış altı öğrencinin parafonksiyonel alışkanlığı yoktu ve %78'inde en az bir adet oral parafonksiyonel alışkanlık vardı; olguların %1,2'sinde on parafonksiyonel alışkanlıkların hepsi vardı ve %22'sinde sadece bir parafonksiyonel alışkanlık vardı. En yüksek sıklıklar bir tarafta sakız çiğneme, bir tarafa doğru uyuma ve kurşun kalem ya da tükenmez kalem çiğneme ile ilgilidir. Deneklerde TME bozukluğu semptom ve bulguları prevalansı şu şekildedir: Eklem çıtlaması (%31), çiğneme kaslarındaki ağrı (%10), gıdaların çiğnenmesi sırasında ağrı (%24) ve ağız açmada ağrı (%14). Sonuçlar, diş kenetlenmesi ve çiğneme kaslarına palpasyon ile hassasiyet arasındaki en büyük ilişkiyi gösterdi. Tüm çiğneme kaslarının palpasyon sırasında en şiddetli ağrı, masseterde temporal kas izledi.

Sonuç: Bu çalışma, deneklerde parafonksiyonel alışkanlıkların en yüksek sıklığının çiğneme sakızıyla ilişkili olduğunu ve en sık görülen TME bozuklukluğu belirtisinin eklem çıtlamaları olduğunu göstermiştir. Buna ek olarak, TME bozukluğu semptomları ile brusizm, tek taraflı çiğneme ve diş kenetlenmesi gibi parafonksiyonel alışkanlıklar arasında anlamlı ilişkiler vardı.

Introduction

Temporomandibular joint (TMJ) disorders are a diverse group of disorders that cause pain and tenderness in the TMJ. Several factors lead to TMJ disorders that consist of erosion, tearing, inflammation and swelling of the joint, trauma, stress, some dental plaques and bruxism and tooth grinding. The pain associated with TMJ disorders might vary from mild to severe. Such disorders might be transient or chronic. Virtually 15% of adults in the US have experienced chronic facial pains (1-3).

Some bad oral habits result in the exertion of abnormal forces to teeth, dental arches and muscles; these habits include nail biting, chewing gums, tooth grinding and playing with the jaws. On the other hand, some studies have reported that TMJ disorders originate from malocclusion, parafunctional habits, stress and trauma (1-4). However, the contribution of each factor to TMJ disorders is still unknown (5-8) because each factor not only contributes to TMJ disorder but also affects other factors, too. For example, if stress is considered a kind of energy, when stressful conditions affect an individual, energy is produced in the body (psycho-physic logical theory) (1).

Each structure in the masticatory system can tolerate the increase in stress, resulting from increased activity of muscles, up to a certain level.

When the stresses exerted on tissues exceed this vital threshold which is referred to as structural tolerance, the process of injury and destruction begins. The first signs of destruction appear in components of the masticatory system that have the lowest level of tolerance. Therefore, the location of the emergence of injury is different from one individual to another individual (1-3).

Deleterious parafunctional habits affect the dentoalveolar structures. If these habits are diagnosed late, resulting in delayed treatment, they will give rise to severe problems which might be irreversible or associated with high costs, difficult technical problems and severe patient suffering.

Therefore, it is necessary to decrease these habits through proper intervention and correct treatment planning, which is not possible without acquiring good statistics. Therefore, the present study was undertaken to acquire data on the prevalence of parafunctional habits and determine their relationship with TMJ disorders in female high school students in Kerman, İran, as a sample of the Iranian population.

Materials and Methods

This study had received ethical approval from Ethics and Research Committee of Kerman University (IR.kmu.ac.ir.1395.34; approval no: 2016/124).

In this descriptive-analytical study, data were collected by completing a checklist in the form of a questionnaire and by carrying out clinical examinations. The questions on the checklist were designed by two pedodontists. Then the checklist was submitted to 5 pedodontists in the faculty of dentistry for evaluation. These pedodontists confirmed that the checklist was favorable. The study population consisted of first- to fourth-grade high school students in Kerman, İran. The aims of the study were explained to all the participants who took part in the study voluntarily. Subjects with severe malocclusion and toothache were excluded from the study. Cluster samples technique was used in the present study. To this end, the high school lists were obtained in Kerman with the cooperation of the city's General Education Organization. Then 8 high schools were randomly selected from each municipal district of the city (2 high schools from each district) as a cluster. Then the questionnaires were explained to the subjects and 368 first- to fourth-grade students in each level completed the questionnaires. Then each student was examined on a conventional chair with the use of a dental mirror, an electric torch, a Vernier caliper (for the evaluation of mouth opening), and a stethoscope (for evaluations of joint sounds) and by palpating the masticatory muscles, while each subject held the questionnaire in her hand.

Before completing the questionnaires, the subjects were informed about the reasons for and the importance of the study and all the variables and factors on the questionnaire were explained to avoid any ambiguities so that the students could complete the questionnaire after completely understanding the importance of the study and the items on the questionnaire. In addition, the aim of the study was individually explained to each student and they were included in the study after they gave their informed consent. In addition, the subjects were reassured that all the data would be kept confidential and the results only would be reported.

Clinical examinations were carried out by one last-year dental student who was trained for one week by one professor in the field in the faculty of dentistry and mastered all the principals of clinical examination. In clinical examinations, first the extent of mouth opening was determined with the use of a Veriner caliper by measuring the distance from the incisal edge of maxillary incisors to the incisal edge of mandibular incisors. Then each subject was asked to open and close her mouth several times so that any joint clicking could be heard with the use of a stethoscope which was placed anterior to the tragus for the evaluation of crepitus and other joint sounds. Then the masticatory mucus was palpated for any tenderness and muscle trismus. In addition, mandibular deviation during mouth opening and closing was evaluated.

Functional Terms

Pain: A feeling of pain anterior to tragus at mouth opening and closing and also during palpation,

Joint sound: Sounds anterior to tragus at mouth opening and closing (crepitus),

Morning headache: Headache in the temporal area at waking up from sleep,

Pain in the ear area: Earache or pain anterior to tragus.

In addition, at the end of clinical examination, a lecture was given to the students who had problems in relation to kicking the habits, the techniques used to kick the habits and the possible future consequences if the habits are not kicked; finally, subjects with problems were referred for treatment.

Protection of human and animal subjects: the authors declare that no experiments were performed in humans and animals.

Statistical Analysis

Statistical analyses were carried out with SPSS 13.5, t-test, chi-squared and ANOVA.

Results

A total of 368 questionnaires were completed in the present study. The mean age of the subjects was

15.0±1.1 years, with an age range of 14-18 years. A total of 66 subjects did not exhibit any parafunctional habits and 78% of the subjects had at least one oral parafunctional habit; 1.2% of the subjects exhibited all the 11 parafunctional habits and 22% of the subject had only one parafunctional habit. The most frequent habits were chewing gums, chewing foods on only one side, sleeping on only one side and chewing pens or pencils (Tables 1, 2).

The prevalence of TMJ disorders in the subjects was as follows: crepitus (31%), pain in masticatory muscles (10%), pain at food mastication (24%) and pain at mouth opening (14%) (Table 3).

Table 1. Distribution of absolute and relative frequency of parafunctional habit

Parafunctional habit	Yes		No	
	n	%	n	%
Chewing gums	302	82	66	18
Chewing cheeks	41	11	327	89
Nail biting	45	12	323	88
Chewing a pen or a pencil	178	48	190	52
Playing with the jaws	25	6	343	94
Leaning the jaw on the hand	112	30	256	70
Leaning the jaw on the arm	21	5	347	95
Tooth clenching	26	7	342	93
Tooth grinding	28	7	340	93
Mastication of food on one side	250	68	118	32
Sleeping on one side	278	75	90	25

Table 2. The relationship between parafunctional habits and symptoms of temporomandibular joint disorders

Parafunctional habit	Symptoms of TMJ disorders					p value
	<3			≥3		
		n	%	n	%	
Chewing gums	Yes	142	39	25	7	0.001
	No	45	12	156	42	
Chewing cheeks	Yes	85	23	36	10	0.021
	No	41	11	206	56	
Nail biting	Yes	58	16	45	12	0.09
	No	15	4	250	68	
Chewing a pen or a pencil	Yes	87	24	54	15	0.001
	No	51	14	176	47	
Playing with the jaws	Yes	49	13	22	6	0.08
	No	21	6	276	75	
Leaning the jaw on the hand	Yes	15	4	41	11	0.040
	No	21	6	291	79	
Leaning the jaw on the arm	Yes	94	26	15	4	0.615
	No	17	5	242	65	
Tooth clenching	Yes	18	5	24	6	0.010
	No	54	15	272	74	
Tooth grinding	Yes	47	13	51	14	0.314
	No	45	12	225	61	
Mastication of food on one side	Yes	91	25	84	23	0.001
	No	25	7	168	45	
Sleeping on one side	Yes	94	26	82	22	0.001
	No	31	8	161	44	

TMJ: Temporomandibular joint

The following results were achieved on the relationship between each parafunctional habit and the presence of at least one of the symptoms and signs of TMJ disorders. There were significant relationships between bruxism, unilateral mastication and chewing gums, pens and pencils, tooth grinding and sleeping on one side and the symptoms and sings of TMJ disorders. In relation to nail biting, too, a relationship was detected with the symptoms and signs of TMJ disorders; however, there were no significant relationships between other habits and symptoms and signs of TMJ disorders (Table 4).

The results of this study showed the strongest relationship between bruxism and palpation tenderness of masticatory muscles (p=0.001). In addition, there were significant relationships between

Table 3. Absolute and relative frequency of symptoms of temporomandibular disorders

Symptom	Yes		No	
	n	%	n	%
Joint clicking	114	31	254	69
Morning headaches	38	10	330	89
Clicking in the ear region	41	11	327	89
Pain in the ear region	28	7	340	92
Muscular fatigue	64	17	304	82
Pain at mouth opening	52	14	316	86
Facial muscle pain	37	10	331	90
Jaw pain at food mastication	88	24	280	76

Table 4. The relationship between parafunction habits with temporomandibular disorder

Parafunctional habit	p value	Correlation coefficient
Chewing gums	0.001*	0.645**
Chewing cheeks	0.341	0.085
Nail biting	0.010*	0. 421**
Chewing a pen or a pencil	0.020*	0.215**
Playing with the jaws	0.214	0.045
Leaning the jaw on the hand	0.317	0.051
Leaning the jaw on the arm	0.09	0.080
Tooth clenching	0.001*	0.345**
Tooth grinding	0.001*	0.189**
Mastication of food on one side	0.001*	0.124**
Sleeping on one side	0.001*	0.254**

*p value <0.05 is significant, **Correlation coefficient t>0.1 is significant

the signs of TMJ disorders and bruxism, unilateral mastication, chewing gums and sleeping on one side only.

The mean extent of mouth opening was 38.0±2.01 mm, with a range of 31-48 mm. The results of this study showed that of all the masticatory muscles, the most severe pain at palpation was related to masseter, followed by the temporalis muscle.

Discussion

TMJ is one of the most complex joints in the human body and is closely related to the profession of dentistry. The disorders of this joint consist of clinical problems that involve the masticatory muscles system and/or the joint itself. Based on the definition provided by the American Dental Association, the symptoms and signs of TMJ disorders consist of pain, tenderness to palpation in TMJ area or masticatory muscles, limitations in the jaw movements, mandibular deviation at mouth opening and closing, and TMJ sounds during mandibular movements (1). The etiologic factors of these disorders have not fully been elucidated and different factors have been proposed. One of the possible predisposing factors is parafunctional habits, which are described as activities of the masticatory system that do not have functional aims and do not play a role in mastication, swallowing and speaking. These habits can lead to trauma since they exert extra loads on the masticatory system. These factors include bruxism, tooth clenching, chewing of hard objects such as pencils, chewing gums, nail biting, sleeping on only one side, habitual chewing of the tongue, lips or cheeks and placing the hand under the chin (1-8).

This study showed that 66 subjects did not exhibit any parafunctional habits and 78% of the subjects had at least one oral parafunctional habit; 1.2% of the subjects exhibited all the 11 para-functional habits and 22% of the subject had only one parafunctional habit. The most frequent habits were chewing gums, chewing foods on only one side, sleeping on only one side and chewing pens or pencils, consistent with the results of other studies. In addition, in a study by Gavish et al. (2), the most important finding was the prevalence of chewing gums (58%). In a study by de Oliveira et al. (9) on 10-12-year-old subjects 47% had at least one oral parafunctional habit. In addition, Schiffman et al. (8) evaluated 269 nursing students, aged 19- 22 years, and reported that the most prevalent habit was chewing gums (87%), with a positive relationship between parafunctional habits and mandibular disorders. Gavish et al. (2) evaluated 248 girls, aged 15-16 years, and reported that the most prevalent parafunctional habit was chewing gums.

Lobbezoo et al. (10) and Restrepo et al. (11) reported that the most prevalent parafunctional habits were bruxism, tooth clenching, tooth grinding and nail biting.

In relation to the prevalence of parafunctional habits, tooth grinding, and chewing were reported in 9.8% and 9.5% of the subjects, respectively. In the study by Choi et al. (12), these prevalence rates were 8.4% and 9.9%, respectively, among 19-year-old Korean subjects.

Therefore, the prevalence of this parafunctional habit is different in different communities, which might be attributed to differences in the study populations in different studies. In addition, factors such as individual's psychological status, habits and sleep status can affect these two factors.

The results of the present study showed that the most prevalent symptoms and signs of TMJ disorders in the subjects were joint sounds (crepitus) (31%), pain in masticatory muscles (10%), jaw pain during food mastication (24%) and pain at mouth opening (14%). In a study by Miyake et al. (13), the most prevalent sign of TMJ disorders was joint crepitus. This study showed significant relationships between nail biting, tooth clenching, unilateral chewing, chewing gums, pens and pencils, tooth grinding and sleeping on one side and the signs of TMJ disorders, consistent with the results of other studies (14).

In a study by Motghare et al. (15), too, there were significant relationships between nail biting, lip biting, tooth grinding and symptoms and signs of TMJ disorders. Based on the results of a study by Alamoudi on 3-7-year-old children, there was a definitive and significant relationship between tooth grinding and TMJ pain, muscle tenderness and limitations in mouth opening (7).

In a study by Sonmez (3) on 182 children aged 5-8 years, there was a definite relationship between thumb sucking and nail biting on one hand and TMJ disorders on the other hand during mixed dentition period. In addition, in a study by de Oliveira et al.

(9) on 10-12-year-old subjects, there was a strong relationship between parafunctional habits and tenderness of masticatory muscles to palpation. Gavish et al. (2) showed significant relationships between chewing gums, playing with the jaws and leaning on the jaw and tenderness of masticatory muscles to palpation and TMJ disorders. However, there was no significant relationship between tenderness to palpation of masticatory muscles and TMJ disorders.

A study by Motghare et al. (15) showed the strongest relationship between clenching and tenderness to palpation in masticatory muscles. In addition, there were significant relationships between tooth clenching, unilateral food chewing, chewing gums and sleeping on one side and the symptoms and signs of TMJ disorders. In a study by Ciancaglini et al. (16), there was a strong relationship between bruxism and the symptoms and signs of TMJ disorders, especially limitation of jaw movements. However, in a study by Choi et al. (12) it was reported that bruxism was not possibly a direct risk factor for inducing TMJ disorders and tooth clenching was considered much more dangerous than bruxism. Furthermore, Pullinger et al. (17) reported a relationship between tooth clenching and pain in facial muscles. In a study by Gavish et al. (2), there was a strong and significant relationship between chewing gums and muscular tenderness and joint clicks. In the present study, too, there was a significant relationship between unilateral chewing and joint pain.

The results of the present study showed that of all the masticatory muscles, the most severe muscular pain at palpation was related to the masseter. In a study by Morrant and Taylor (18) in Glasgow University, 18% of the subjects exhibited pain and muscle tenderness in the masseter muscle during palpation. In a study by Agerberg and Inkapool (19), muscle pain was the most severe in the temporalis muscle.

Conclusion

The results of the present study showed that the highest frequency of parafunctional habits was related to chewing gums and the most frequent sign of TMJ disorder in the subjects was joint clicks. In addition, there were significant relationships between all the symptoms and signs of TMJ disorders and the parafunctional habits of bruxism, unilateral mastication and tooth clenching.

Ethics

Ethics Committee Approval: For study, approval of Ethics Committee of Kerman University of Medical science was obtained (approval no: 2016/124).

Informed Consent: Protection of human and animal subjects: The authors declare that no experiments were performed in humans and animals.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: M.A.H., Concept: M.A.H., Design: M.A.H., Data Collection or Processing: F.M., Analysis or Interpretation: A.M., Literature Search: F.M., Writing: M.A.H., A.M.

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Case Report / Olgu Sunumu

Peroneal Nerve Palsy due to Synovial Cyst of Proximal Tibiofibular Joint

Proksimal Tibiofibular Eklemin Sinovyal Kistine Bağlı Gelişen Peroneal Sinir Felci

Işıl Karataş Berkit[1], Yasemin Turan[2], Kevser Bayraktar[2]

[1]Aydın State Hospital, Clinic of Physical Medicine and Rehabilitation, Aydın, Turkey
[2]Adnan Menderes University Faculty of Medicine, Department of Physical Medicine and Rehabilitation, Aydın, Turkey

Abstract

Synovial cysts are benign soft-tissue tumors that arise from synovial joints or tendon sheaths. Synovial cyst of proximal tibiofibular joint is a very rare condition, which is included in non-traumatic causes of peroneal nerve palsy. This article presents clinical, and radiological findings of peroneal nerve palsy in a 50-year-old male patient admitted with sudden drop foot. Based on the clinical examination, electroneuromyography data, magnetic rezonans image the compression of nerve by synovial cyst was confirmed. Peroneal nerve palsy was completely improved after surgical resection of synovial cyst and physical theraphy and rehabilitation. In conclusion, synovial cysts of proximal tibiofibular joint causing peroneal nerve palsy should be remembered as a possible differential diagnosis for patient with drop foot.

Keywords
Synovial cyst, drop foot, peroneal nerve palsy

Öz

Sinovyal kistler, sinovyal eklemlerden veya tendon kılıflarından köken alan iyi huylu yumuşak doku tümörlerindendir. Proksimal tibiofibular eklemin sinovyal kisti, peroneal sinir felcinin nadir görülen travma dışı nedenleri arasında yer almaktadır. Bu yazıda aniden düşük ayak gelişen 50 yaşındaki erkek hastada proksimal tibiofibuler eklemin sinovyal kistine bağlı peroneal sinir felcinin klinik ve radyolojik bulguları sunulmuştur. Temel olarak, klinik muayene, elektronöromiyografik inceleme magnetik rezonans görüntüleme ile sinovyal kistin baskıya neden olduğu ortaya konmuştur. Sinovyal kistin cerrahi çıkarımı ve fizik tedavi ve rehabilitasyon uygulamaları sonrası olgunun klinik bulguları geriledi. Sonuç olarak düşük ayak gelişen olgularda proksimal tibiofibular eklemin sinovyal kistine bağlı peroneal sinir felci gelişebileceği akılda bulundurulmalıdır.

Anahtar Kelimeler
Sinovyal kist, düşük ayak, peroneal sinir felci

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Address for Correspondence/Yazışma Adresi:
Işıl Karataş Berkit MD, Aydın State Hospital, Clinic of Physical Medicine and Rehabilitation, Aydın, Turkey
Phone : +90 256 213 90 00
E-mail : isilkaratasberkit@yahoo.com.tr
ORCID ID: orcid.org/0000-0002-0401-5248

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Introduction

Peroneal nerve palsy occurs because of the fact that peroneal nerve is subject to pressure and direct trauma in fibula head and neck length especially where it is the most superficial (1-4). Mostly traumatic reasons cause this pressure (4,5). As a result of total knee arthroplasty or arthroscopic intervention to the knee, this nerve may be damaged. Casts, leg orthesis, high boots, tight socks and sitting by crossing

legs for a long time may result in pressure for nerve. Moreover, remaining in improper position for a long time during anesthesia may cause nerve pressure (3-5). One of the rare reasons is ankle injury in inversion position (1,2). Peroneal neuropathy occurring as a result of weight loss was reported in literature. Also peroneal neuropathies due to tumor or cysts were reported even rare (4,5). Synovial cyst of proximal tibiofibular joint is among the non-trauma reasons of peroneal nerve palsy which is rarely seen. Synovial cyst is known as the most common cystic formations seen in upper extremity. It is known as benign soft tissue tumor originating from popliteal fossa generally in lower extremity. Synovical cysts occur in proximal tibiofibular joint very rarely and cause peroneal nerve pressure and neurological symptoms (6). Sultan identified peroneal nerve neuropathy due to synovial cyst in a case in 1921 for the first time (7). In magnetic resonance imaging (MRI) studies synovial cyst of proximal tibiofibular joint was observed in 0.03% of cases having symptomatic knee lesion (8,9). It is recommended for the cases of peroneal nerve palsy due to synovial cyst of proximal tibiofibular joint in the literature that in addition to anamnesis and physical examination, electromyography (EMG) examination should be performed and knee circle should be examined with MRI for the presence of synovial cyst (1-9). In the cases having peroneal nerve palsy due to synovial cyst of proximal tibiofibular joint, if symptoms do not regress following 3-4 month conservative treatment and adequate recovery is not achieved, nerve decompression and cyst excision is recommended (2,9-11). In this paper, a case having peroneal nerve palsy due to synovial cyst of proximal tibiofibular joint is presented guided by the literature.

Case Report

Fifty-year-old male patient having the complaint of paresthaesia in right cruris lateral for the last three weeks and having sudden weakness of right ankle 10 days ago applied to our polyclinic. The patient who was a farmer did not have lumbar pain and trauma history. He did not describe a characteristic related to the presence of autoimmune rheumatic diseases in personal and family history. In the physical examination of the case, steppage gait was determined by inspection. Sensitivity of right fibula head was present with palpation. At the same time, Tinel test performed to this region was positive. In neurological examination, hypoesthesia was present in right leg lateral, muscle strength of right ankle dorsiflexion, toe dorsiflexion and ankle eversion was at the level of 0/5. Acute partial denervation findings were detected in distal innervation muscles of peroneal nerve in EMG. Cyst formation having T1 hypointense and T2 hyperintense appearance being about 11 mm in diameter was observed near the proximal tibiofibular joint (Figure 1). The case getting the diagnosis of peroneal nerve palsy due to synovial cyst of proximal tibiofibular joint with these findings, first we decided to treat by conservatively after then if there was not enough improvement we planned to use surgical treatment. Non-steroidal anti-inflammatory drugs, vitamin B and foot-ankle orthesis were prescribed to the case. A physical therapy program comprising of 30-session electric stimulation to ankle evertors with ankle and toe dorsiflexors and strengthening exercise was performed. It was observed in the end of the treatment that hypoesthesia continued by reducing and muscle strength of ankle dorsiflexion, toe dorsiflexion, ankle eversion increased to 2/5. It was noted that there was no sensitivity with palpation and Tinel test was negative in the examination of the patient. The patient was followed by us clinically. In month 1 and 3 control examinations of the patient following the treatment, more functional improvement

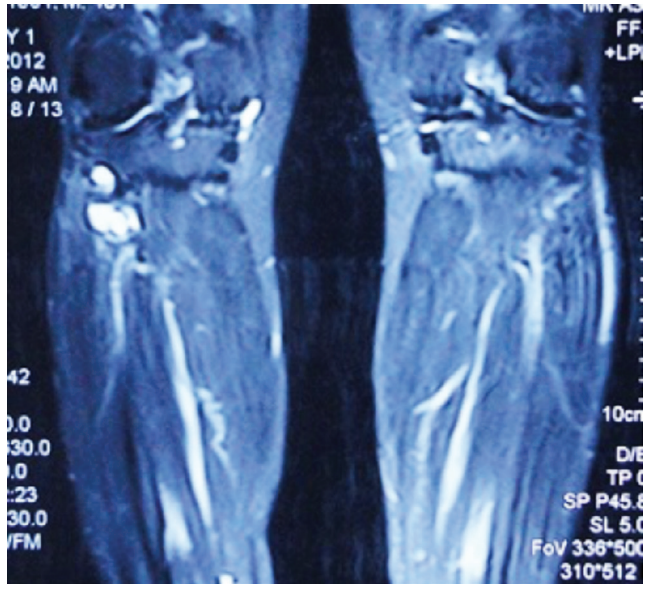

Figure 1. In knee magnetic resonance imaging of the case presented, hyperintense synovial cyst in T2-weighted section is seen

was not detected and therefore operation decision was made as a result of consultation of orthopedia clinic. In post-op month 3 control examination of the patient having synovial cyst excision, it was observed that hypoesthesia regressed completely and muscle strength of ankle dorsiflexion, toe dorsiflexion, ankle eversion increased to 4+/5. Our case was followed by us with home exercise program involving lower extremity strengthening exercises. In post-op month 6 examination, a pathological finding was not observed in EMG and MRI.

Discussion

When sciatic nerve leaves from popliteal fossa, it branches to peroneal nerve. This nerve passes behind fibula head and through fibular tunnel, it branches as superficial and deep and progresses (3-5). The most frequent peripheral nerve injury in lower extremity multiple traumas is peroneal nerve damage (5). It is mostly injured in the level of fibula head it progresses very superficially mostly or exposed to pressure. This pressure arises from traumatic reasons mostly. Traumatic reasons include proximal fibula and distal femur fractures, knee dislocations, tibial osteotomy, total knee arthroplasty, knee arthroscopy, laceration, post-operative suture pressure (1,3). Non-traumatic reasons include external or internal pressure to peroneal nerve. They also include crossing legs, squatting for a long time, casts, leg orthosis, elastic tight bandages, high boots, tight socks or trousers, extremity traction slings, excessive or long-term tourniquet use (4,5,9). In addition to these reasons, long-time ice application to knee lateral for cryotherapy, improper lying position of the patients being immobile for a long time or during anesthesia and increase of sensitivity to pressure as adipose tissue in the fibula head reduces as a result of excessive weight loss are among the reasons resulting in external pressure (12). Intraneural and extraneural tumors, hypertrophy seen in athletes in muscles, ganglion of tibiofibular joint, peroneal vascular aneurism, osteochondroma of proximal tibia and fibula, aneurismal bone cyst are the reasons of internal pressure. Peroneal nerve palsy is seen in systemic diseases such as hyperthyroidism, diabetes mellitus, vasculitis and leprosy (13,14). Other very rare reasons include extending legs procedures, anorexia nevrosa, paraneoplastic syndromes, injury of ankle in inversion position and peroneal neuropathies due to synovial cyst as our case (1,2,6,8,9,15). In a study conducted by Hersekli et al., (9) it was indicated that synovial cyst presence in proximal tibiofibular joint was defined by Lenander in 1891 for the first time and total 53 cases were reported from that date to 2004. It was demonstrated that 28 of 53 cases had peroneal nerve palsy (9). We observed that 16 cases were reported from 2004 until today as a result of our analysis with the expression of “synovial cyst of proximal tibiofibular joint” in our literature scan (2,9,15-20). As a conclusion, there are total 45 cases having peroneal nerve palsy due to synovial cyst of proximal tibiofibular joint with our case in the literature.

Three different cases having synovial cysts but offering different clinic appearance were presented in the publication of Mortazavi et al. (15). Synovial cyst is asymptomatic of the first one of these three cases and it is sometimes symptomatic in the second case and it resulted in hypoesthesia in foot lateral and drop foot in the third case like our case. EMG and MRI examinations were used for diagnose of these cases and synovial cyst was resected in all of them as the treatment (15). In the review of Hersekli et al., (9) three cases having the diagnosis of peroneal nerve palsy due to synovial cyst of proximal tibiofibular joint were presented. All of three cases had drop foot and all cases were operated. Our case had neurological symptoms such as drop foot and hypoesthesia in right leg lateral similar to the literature. Synovial cyst of proximal tibiofibular joint should be considered for differential diagnosis of drop foot. History and physical examination are guiding for the diagnosis of peroneal nerve palsy. Ankle weakness, hypoesthesia of cruris lateral in the history and loss of strength in ankle dorsiflexion, in toes extension in the physical examination, steppage gait and positive result of Tinel test at the level of fibula head make us consider the possibility of peroneal nerve palsy (6). EMG is used to determine the location, severity and phase of the lesion for the diagnosis. Direct graphies, computerized tomography and MRI examinations are useful for the patients getting the diagnosis of peroneal nerve palsy for analyzing the etiology. Direct graphies are used to show underlying fracture, bone tumors or deformities. Tumors leading to compression, lesions such as cyst can be examined in detail by these methods (3,4,5,21). The final diagnosis of our case was established with MRI method. In a retrospective study carried out by Kim et

al., (19) benefits of MRI findings to detect the etiology in 11 patients with the diagnosis of non-traumatic peroneal nerve palsy were analyzed. While the exact diagnosis can be established by physical examination and EMG in all of these patients, etiology of peroneal nerve palsy became prominent in 9 cases with MRI. For this reason, MRI was shown to be more valuable methods than other methods for the diagnosis of these patients (19). In the light of this information, imaging methods involving tibiofibular joint should be used to look for the presence of synovial cyst and to eliminate especially S1 radiculopathy differential diagnosis for the patients applying with drop foot.

First of all, conservative treatment methods should be applied for the treatment of peroneal nerve palsy. It should be aimed that mobility of the patient is ensured and they gain the functions again. Non-steroidal anti-inflammatory drugs and oral corticostreoids, being medical therapy agents are used to control the inflammatory process (1,15). Cyst aspiration and steroid injection can be applied to patients not having neurological symptoms; however rate of relapse of cyst is high for this treatment (9). Tricyclic anti-depressant and antiepileptic agents such as gabapentin and pregabalin contribute to the treatment for the patients having pain and paresthaesia. Foot-ankle orthesis or orthopedic shoes can be used for gait disorders. Physical therapy agents and exercise treatment are beneficial for regaining function. Electric stimulation, one of the physical therapy agents is the therapy method applied to strenghten muscles innervated by peroneal nerve. Strenghtening exercises are useful to increase decreased muscle strenght (22). Non-steroidal anti-inflammatory drug and vitamin B was initiated to our case as the medical therapy. Foot-ankle orthesis was prescribed because of having gait disturbance and steppage gait. Electric stimulation and strengthening exercise was applied to ankle evertor muscles and ankle and toe dorsiflexor muscles. In the end of the therapy, muscle strength of ankle dorsiflexion, toe dorsiflexion, ankle eversion increased to 2/5. Three months after rehabilitation there was not any recovery in our patient so synovial cyst excision was performed. It was indicated that complete recovery could be achieved for functions in forth month of the operation in the case of peroneal neuropathy due to synovial cyst of proximal tibiofibular joint presented by Greer-Bayramoğlu et al. (22). Clear recovery in month 3 following the operation observed in our case like the literature results. While there is not an exact consensus related to the treatment of this rare case, if neurological symptoms do not regress in month three and four in spite of the conservative treatment, it has been reported that the best treatment option is cyst resection (1,9,21). Fabre et al. (23) showed that post-operative motor recovery was 87% in a study performed with 60 peroneal nerve palsy patients. In a case report, synovial cyst recurrence was observed 18 months after the operation in a case and drop foot of one case did not improve (9). It should be considered that recurrence less than 10% can occur following cyst resection (6). Recurrence was not seen in post-operative month 6 in our case. As a conclusion, peroneal nerve palsy due to synovial cyst of proximal tibiofibular joint observed very rarely in drop foot patients should be taken into consideration. Moreover, this region should be examined with MRI to establish a diagnosis. Improvement of functions of the patients should be followed with control examinations closely and should be evaluated for the requirement of surgical operation.

Ethics

Informed Consent: We received indormed consent from the patient.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Y.T. Concept: K.B. Design: Y.T. Data Collection or Processing: I.K.B. Analysis or Interpretation: Y.T. Literature Search: I.K.B. Writing: I.K.B.

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Case Report / Olgu Sunumu

A Rare Cause af Solid Mass in the Head and Neck Area and Kimura's Disease as a Diagnostic Dilemma

Baş ve Boyun Bölgesinde Nadir Bir Kitle Nedeni ve Tanısal Karmaşa Olarak Kimura Hastalığı

Mustafa Şahin[1], Raşit Midilli[2], Mine Hekimgil[3]

[1]Adnan Menderes University Faculty of Medicine, Department of Otorhinolaryngology, Aydın, Turkey
[2]Ege University Faculty of Medicine, Department of Otorhinolaryngology, İzmir, Turkey
[3]Ege University Faculty of Medicine, Department of Pathology, İzmir, Turkey

Abstract

Kimura's disease which is known as a self-limited chronic inflammatory disease with unknown etiology, that can be easily misdiagnosed, causing long standing tumor-like painless nodules in the subcutaneous tissue, localized especially in the head and neck region. It has usually good prognosis. Common characteristic features of Kimura's disease were peripheral eosinophilia and increased serum immunoglobulin E levels. Typical histological features of the lesions are prominent eosinophilic and lymphocytic infiltration and fibrosis. The aim of this case report was reminding the Kimura's disease, clinical features and treatment have been determined with the case reports, with the findings of a 43 years old woman and associated literature data.

Keywords
Kimura's disease, head and neck, neck mass

Öz

Kimura hastalığı; tanısı oldukça zorlayıcı olabilen, deri altı dokuda uzun süreli, tümör benzeri ağrısız nodüllerle seyreden, özellikle baş-boyun bölgesinde yerleşen, iyi seyirli, kendini sınırlayan ve nedeni bilinmeyen kronik enflamatuvar bir hastalıktır. Laboratuvar bulgularında bu hastalığa spesifik bir özellik tanımlanmamıştır. Sıklıkla periferik kanda eozinofil artışı ve serumda artmış immünoglobulin E düzeyi birliktelik gösterir. Lezyonların tipik histolojik özellikleri belirgin eozinofilik ve lenfositik infiltrasyon, vasküler proliferasyon ve fibrozistir. Cerrahi eksizyon tanısal olabileceği gibi aynı zamanda tedavi edici de olabilmektedir. Bu makalede; şimdiye kadar klinik özellikleri ve tedavisi olgu sunumları ile belirlene gelmiş Kimura hastalığının, 43 yaşındaki bir kadın hastanın bulguları literatür bilgileri eşliğinde tartışılarak, tekrar hatırlatılması amaçlandı.

Anahtar Kelimeler
Kimura hastalığı, baş ve boyun, boyun kitlesi

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Address for Correspondence/Yazışma Adresi:
Mustafa Şahin MD,
Adnan Menderes University Faculty of Medicine, Department of Otorhinolaryngology, Aydın, Turkey
Phone : +90 533 654 55 02
E-mail : mustafa.kbb@gmail.com
ORCID ID: orcid.org/0000-0002-9009-6389

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Introduction

Kimura disease (KD), which is one of the most difficult clinical entities concerning the diagnosis, is a rare, benign, chronic inflammatory disease with unknown etiology. It is most commonly reported in young-middle-aged men generally as palpable lymph nodes on head and neck region and mass lesions located commonly

on large salivary glands, subcutaneous tissue and rarely on oral (1). There may be single or widespread lesions on the body; spontaneous remission may be seen, and the disease may also recur after months or years. In literature, it has many different names including, eosinophilic granuloma of lymph nodes and soft tissue, eosinophilic hyperplastic granuloma, angio-lymphoid hyperplasia (ESAH) with eosinophilia (1,2). It was assumed to be developed as a result of self-limited autoimmune or allergic reactions triggered by an unknown agent (1). Although any specific laboratory finding was not defined, there may be eosinophilia on peripheral blood and tissues and an increase on serum immunoglobulin (Ig) E levels (2). In some previous reports; eosinophilia on peripheral blood or tissues, increase on serum IgE levels and soft tissue masses on head and neck region accompanied by recurrent lymphadenopathies for a long time has been defined as the characteristic triad of the disease (2,3). Though many advanced investigations performed, this disease may not be diagnosed and the most important point for the diagnosis is the histopathological evaluation of tissue samples characterized by infiltration of lymphoid follicles by dense eosinophilic-lymphocytic inflammation, fibrosis and vascular proliferation (4). It may show spontaneous remission but may also recur after months and even after years. There is not a consensus about the treatment of this disease. Surgical excision is diagnostic and in some conditions, it may also be curative but ablative surgery should be avoided. In this disease that may show recurrences commonly, other treatment strategies include radiotherapy, systemic steroids, cyclosporine, pentoxifylline and some cytotoxic agents (1,3).

Case Report

A 43-yr-old female patient was admitted with progressive, painless, widespread swellings on neck region for about 7 months. It was learnt that similar swellings also developed about 3 years ago from her history; but they could not be diagnosed though detailed laboratory examinations including complete blood count, peripheral blood smear, general biochemical panel, chest graph, serum viral serology, purified protein derivative (PPD) test, neck and abdominal ultrasounds and also fine needle aspiration biopsy (FNAB) obtained from one of the masses located on neck region were performed. At that time, except 1000 mg amoxicillin-clavulanic acid combination she took at the very beginning of her symptoms for about 2 weeks, she did not take any other medical treatments and her symptoms resolved spontaneously. In her history, she reported appendectomy about 14 years ago and cholecystectomy 4 years ago without any known chronic illnesses or long-term medications. Complete head and neck physical examination including endoscopic investigations and systemic general physical examination were unremarkable except painless lymphadenopathies, determined on neck palpation at submandibulary region and on 2nd level bilaterally with a maximum diameter of 2.5 cm. They were having rubber consistency and covered with normal skin. Later, laboratory investigations were performed step by step including complete blood count, general biochemical panel, chest graph, serum viral serology, serological tests for toxoplasmosis and syphilis, PPD test, peripheral smear, thyroid function tests, rheumatologic serum markers such as antinuclear antibody, cytoplasmic anti-neutrophil cytoplasmic antibody, rheumatoid factor, sedimentation, serum IgG, A, M, E levels, neck and abdominal ultrasounds and computed tomography (CT) of neck region. In peripheral smear; on leucocyte formulation there were 16% of eosinophil and the absolute eosinophil count was determined as 1696. Serum IgE level was 876 IU/mL (the upper limit was 100 IU/mL). Neck ultrasound and CT revealed that there were many, diffuse, heterogeneous, and oval in shape, smooth bordered lymphadenopathies with a maximum diameter of 3 cm on submandibular, parotid and jugulodigastric regions bilaterally. Histological evaluation of FNAB material obtained from one of the masses located on neck region revealed benign cytology with ordinary lymphoid cell communities. Since a certain diagnosis could not be achieved with all those investigations, histopathological examination of 2 neighbor lymph nodes excised from the submandibular region was performed for both the diagnosis and exclusion of malignancy. In this evaluation, there were follicular lymphoid hyperplasia with obvious germinal centers, enlargement in paracortical space, post-capillary venule proliferation, eosinophil infiltration and eosinophilic micro-abscess foci with normal distribution of T and B lymphocytes in histochemical investigations with CD3 and CD20. On

para-follicular region there were rarely CD30 positive active lymphoid cells, CD15 was negative, obvious capillary vessel network proliferation was determined with CD31 and CD34, evident increase in mast cells was determined with CD117 and mast cell tryptase, IgE positive plasma cells in germinal centers were defined and all those findings were compatible with the diagnosis of Kimura lymphadenopathy (Figure 1). Follicular hyperplasia with obvious germinal centers and eosinophilic infiltrate covered with fibrous tissue were determined (Figure 2). The patient was informed in detail after the diagnosis of KD, and she was advised the treatment methods recommended in literature including intralesional and systemic steroid treatment, radiotherapy and treatment with some cytotoxic agents; surgical treatment was also explained but since the lesions were widespread on neck region surgical excision was not recommended as the first treatment method. The patient accepted the systemic steroid treatment that will be started with a dose of 1 mg/kg, then will be reduced in 10 days and continued with 4 milligrams for 2 months as maintenance treatment; but she left the treatment voluntarily. About 15 months after the diagnosis, there was not any progression on her symptoms, physical examination or laboratory findings and there was a regression on diameters of lymph nodes located on neck. The patient was informed about the announcement of her data regarding the disease and treatment, and her verbal and written informed consents were obtained.

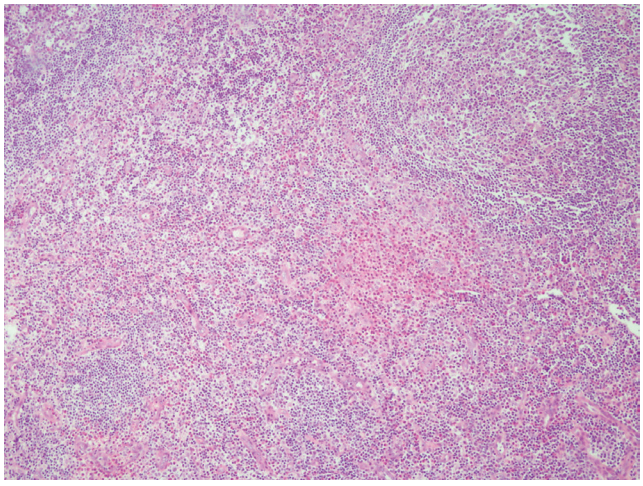

Figure 1a. In lymph node, obvious follicular hyperplasia and dense eosinophilic leucocyte infiltration on paracortex with postcapillary venule proliferation (hematoxylin and eosin, x10)

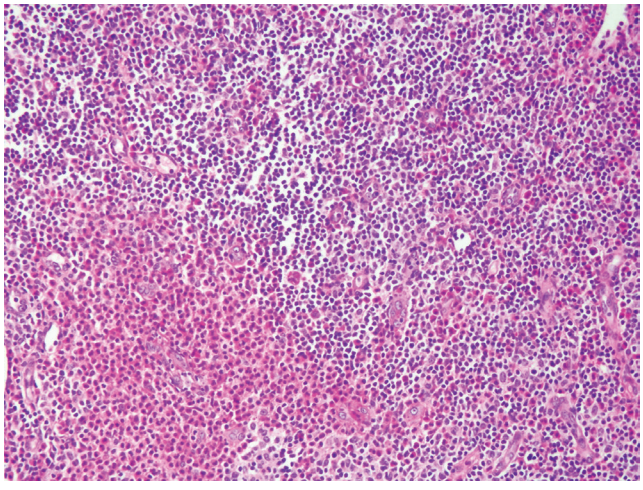

Figure 1b. Eosinophilic micro-abscess development on paracortex (hematoxylin and eosin, x20)

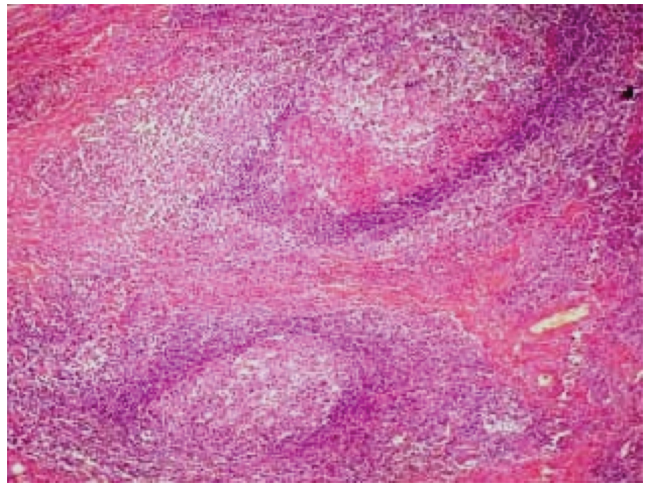

Figure 2. Interstitial fibrosis and lymphoid follicles with obvious germinal centers (hematoxylin and eosin, x10)

Discussion

This disease, which is first defined in China in 1937 by Kim and Szeto, took its place in literature with its today known name in 1948 after systematic investigations performed by Kimura et al. (5). In definition of this disease, based on its histopathological features, some terms such as eosinophilic granuloma, eosinophilic hyperplastic granuloma, angio-lymphoid hyperplasia with eosinophilia of lymph nodes and soft tissue were used and until 1994, totally 120 cases, most of which were from Asia, were reported in literature (2,6). It is generally reported in middle-ages, with a male/female ratio of 4/1 among diagnosed patients, and more

commonly described in Asia. It is usually determined as painless tumor-like subcutaneous mass or regional lymphadenopathy on head and neck region. In some cases, local or widespread itching or subacute or chronic dermatitis associated symptoms, brick reddish papules on skin or subcutaneous nodules may accompany (1,2). In a number of patients proteinuria due to nephrotic syndrome may be determined (7). In this reported case, there was not any complaint except swelling on neck and also there was not any finding on physical examination except widespread masses on neck. Although, in pathophysiology of the disease, allergic or autoimmune reactions triggered by an unknown agent have been suspected, in general its etiology is not identified and it is self-limited. Although not defined exactly, in disease development some theories such as corrupted T-cell immune-regulation or triggered IgE-mediated type 1 hypersensitivity reaction by *Candida albicans*, viruses, parasites or neoplasia resulting in increased secretion of eosinophil-trophic cytokines including interleukin 4-5-6 and eosinophilic cationic protein were proposed (1-4). In immunohistochemical investigations skin, lymph nodes and peripheral blood were determined to be rich in HLA-DR CD4 cells (4). In evaluation of disease activity, increase in eosinophilic cationic protein levels may be used. In 30-80% of patients with KD eosinophilia in peripheral blood, and increased serum IgE levels in some cases may be present (8). In our case report there were also peripheral eosinophilia and increased serum IgE levels present. In histopathological evaluations, lymphocytic infiltrations forming lymphoid follicles and within the follicles eosinophils, vascular proliferation, dense endothelial venules and fibrosis were observed (1,4,9). Histopathological evaluation of our patient was concomitant with the features defined in literature and those features are the main diagnostic tool. Overlap of the disease symptoms with the symptoms of many other diseases, generally normal advanced and detailed laboratory investigations, absence of the definition of specific features of this disease, as mentioned previously absence of eosinophilia or IgE increase in tissue or blood in many patients, and lack of diagnosis even with the histopathological evaluations of tissue samples cause the diagnostic procedure of this disease to be very difficult putting the clinicians in a challenging situation in the face of the patient (2,6,8). Before the diagnosis of KD, the patients are exposed to many laboratory tests for the differential diagnosis of mass lesions on neck region. Radiological investigations are insufficient for the diagnosis but may especially give data about the spread of the disease. Some specific features of KD were reported on CT and the magnetic resonance imaging (MRI) (10). In both imaging methods, the most common findings on head and neck region are enlarged salivary glands or increased salivary gland masses with enlarged lymph nodes. In KD, increased contrast enhancement in CT in affected lymph nodes and parotid gland, and elevated signal involvement may be observed in T1 and T2 weighted scans of MRI (11). The most valuable method in diagnosis is the histopathological evaluation of tissue and affected lymph node excisional biopsy material. Since it is almost impossible to make an exact diagnosis without biopsy, surgical procedures are required in many patients. FNAB of the mass is not diagnostic and for that reason surgical biopsy of the mass is mandatory (2,6). Histopathological characteristic feature of KD is the presence of obvious germinal centers with dense IgE networks composed of cellular, vascular and fibrous components in affected lymph nodes, that was shown with immunoperoxidase studies. Cellular features of germinal center include dense eosinophilic infiltrations with eosinophilic micro-abscess, enclosing necrosis on centers and dense lymphocytes and plasma cells on background (2-6,8). Similarly, in our case, the most important reasons for performing that much laboratory investigations for the diagnosis were; lack of determination of specific features of KD yet, generally lack of any symptoms of patients except swelling on neck, determination of laboratory investigations performed to the patients usually normal, lack of presence of elevated absolute eosinophilia count and/or serum IgE levels in many patients, and requirement of exclusion of many other disease in differential diagnosis. The main diseases that should be excluded are some malign diseases such as lymphoma, Kaposi's sarcoma, angiosarcoma, neck metastasis of malign tumors, dermatofibrosarcoma protuberance, cylindroma as well as some benign conditions such as hemangioma, pyogenic granuloma, Kikuchi disease, Mikulicz disease, angio-immunoblastic lymphadenopathy, ESAH and parasite diseases such as toxoplasmosis that may also cause

increases in serum IgE levels and blood eosinophil counts (2-4,8,11). KD may mimic many diseases such as Mikulicz disease, eosinophilic granuloma, lymphoma, salivary gland tumors and ESAH (2,4). ESAH, that was previously regarded as the same disease with KD, in fact is the most commonly confused disease with KD. Dissimilar with KD, ESAH is a vascular tumor most commonly reported in women with advanced ages in Western Communities. Moreover, in ESAH lymphadenopathy is not common, there are many predominant, small erythematosus dermal papule or nodules present on head-neck region and peripheral eosinophilia (in general less than 10%) is not common with normal serum IgE levels (2,4,9). The diagnosis may be established on the basis of the biopsy with the clinical features, peripheral eosinophilia and elevated serum IgE levels in KD; however, despite all detailed methods, the disease may not be diagnosed. In ESAH, infiltration is more diffuse with less fibrosis, and germinal centers are not reported commonly but endothelial alterations are obvious in histological investigations (4,9).

Up to date, any malign transformation of KD was not reported in literature. One of the many unknowns about the disease is the development of some renal diseases that may cause Nephrotic syndrome with a rate of 5-15% in KD (7). In 12-16% of patients, proteinuria may be determined. It is clearly known that, steroids are used as immunomodulator agents in treatment of both nephrotic syndrome and the KD (12). At that point, our patient was also followed-up in nephrology department concomitantly, and renal involvement was not determined. Moreover, although involvement of major salivary glands and oral mucosa is also possible in KD, in our case major salivary glands or oral mucosa was not involved. We also investigated the lymph nodes, bone marrow, thorax, gastrointestinal system in detail, and did not determine any other accompanying pathology. Although the treatment after the diagnosis of the disease is still controversial, age and general health status of the patient as well as the spread and localization of the disease should be considered (1,2). Diagnostic surgical excision for the isolated lesions may also be therapeutic at the same time; nevertheless, since autoimmune and hypersensitivity reactions are accused in pathophysiology, systemic or local intralesional steroid treatment is more commonly accepted. If the general condition of the patient does not let those treatments, or if the disease is highly widespread, another option is the radiotherapy (6,11). It should be kept in mind that, this is a self-limited disease and malign transformation is not defined before. If the differential diagnosis from the possible malign lesions could be performed, as much as possible consideration of conservative treatments are advised (1,3). For example, in critical lesions located near to some organs such as eyes, destructive treatment methods such as surgery or radiotherapy should be avoided. Unlike with those classical treatments, especially in patients with accompanying Nephrotic syndrome, some immune modulator agents such as trans-retinoic acid, cyclophosphamide, chewable nicotine tablets, vincristine, imatinib and leflunomide were practiced but adequate experience is not present about those treatments (11,12). Although KD is a very well-known disease in pathology community since it has been discussed between the pathologists for long years, unfortunately, it is obvious that among ear, nose and throat physicians the data about this relatively rare disease is very limited and sufficient interest and awareness for KD is not present in that group. In conclusion, with this manuscript, we aimed to re-arouse the interest to the KD, the diagnosis of which may be very problematic for both the patients and the physicians, that may have many clinical pictures and by this way we emphasized the requirement for more certain algorithms in diagnosis and treatment of this disease with larger case series and reviews.

Ethics

Informed Consent: Patient was verbally informed about this scientific article and signed an informed consent form.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: R.M., M.Ş., Concept: R.M., M.Ş., M.H., Design: M.Ş., M.H., Data Collection or Processing: M.Ş., Analysis or Interpretation: M.Ş., R.M, M.H., Literature Search: M.Ş., R.M., M.H., Writing: M.Ş., R.M., M.H.

Conflict of Interest: No conflict of interest was declared by the authors.

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Case Report / Olgu Sunumu

Poland Syndrome and Pregnancy

Poland Sendromu ve Hamilelik

Emre Zafer, Selda Demircan Sezer, Sümeyra Nergiz Avcıoğlu, Burcu Bıçakçı

Adnan Menderes University Faculty of Medicine, Department of Obstetrics and Gynecology, Aydın, Turkey

Abstract

Poland syndrome is a rare congenital disorder presenting with absence of unilateral thoracic muscles. Upper extremity, rib and connective tissue deformities usually accompany muscle agenesis or hypoplasia on the same side. Although its etiology remains unknown, inadequate perfusion is suspected for related regional tissue hypoplasia/aplasia. There is scarce information about possible cardiopulmonary function involvement due to abnormal thoracic muscle and tissues. A slight change in this function may be worsened in pregnancy affecting maternal and fetal health. Here we present a 30 weeks pregnant patient with Poland syndrome who developed severe shortness of breath and eventually had to have iatrogenic preterm delivery. Rare syndromes compatible with life and reproduction can be a challenge for clinicians especially during pregnancy due to unpredictable effects on gestational physiologic adaptation processes. Therefore, case reports or series regarding pregnancy complications of these rare syndromes provide valuable information for possible complications and their management options.

Keywords
Poland syndrome, pregnancy, preterm

Öz

Poland sendromu tek taraflı göğüs kas deformiteleri ile seyreden konjenital bir hastalıktır. Genellikle aynı taraf üst ekstremite, kaburga ve bağ dokusu deformiteleri, kas agenezileri veya hipoplazilerine eşlik eder. Etiyolojisi hala belirsiz olsa da etkilenmiş bölgelerin yetersiz ve defektif perfüzyonunun bölgesel doku hipoplazi ve aplazisine yol açtığı düşünülmektedir. Kardiyopulmoner fonksiyonun göğüs kafesi kas ve doku anormalliğine bağlı etkilenme düzeyi ile ilgili çok az bilgi vardır. Bu fonksiyondaki hafif sayılabilecek değişiklikler gebelik döneminde maternal ve fetal sağlığı etkileyebilecek düzeyde kötüleşebilir. Burada Poland sendromu olan 30 haftalık gebelikte şiddetli nefes darlığı şikayeti nedeniyle iyatrojenik preterm doğum olgusu sunulmaktadır. Hayatla bağdaşan ve üreme fonksiyonunun korunduğu sendromlar özellikle hamilelik dönemlerinde fizyolojik adaptasyon süreçleri üzerinde öngörülemez etkileri nedeniyle klinisyenler için zorluk oluştururlar. Bu nedenle nadir sendromların hamilelikte görülen komplikasyonlarına dair olgu sunumları beklenen olası sorunlar ve yönetim biçimleri hakkında değerli bilgiler sağlar.

Anahtar Kelimeler
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Address for Correspondence/Yazışma Adresi:
Emre Zafer MD,
Adnan Menderes University Faculty of Medicine, Department of Obstetrics and Gynecology, Aydın, Turkey
Phone : +90 530 435 89 09
E-mail : dr.emrezafer@gmail.com
ORCID ID: orcid.org/0000-0001-9262-2947

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Introduction

Poland syndrome (OMIM 173800), a rare congenital syndrome with incidence between 1/10.000-100.000, was first described by Alfred Poland in 1841 (1,2). It consists of unilateral aplasia/hypoplasia of pectoralis major muscle and accompanying defects of other thoracic muscles, ribs, and/or ipsilateral upper extremity at varying frequency

and degrees (2). Among these abnormalities, it is plausible to expect that some of these can cause respiratory function problems under certain conditions like anesthesia and pregnancy: dextrocardia, scoliosis, pectus carinatum, pectus excavatum, lung herniation, paradoxical respiration (3). Our pregnant case did not have neither of the latter, however her respiratory complaints were severe enough to cause iatrogenic preterm delivery.

Case Report

A written informed consent was obtained from patient for this presentation. An 18-yr-old gravida 1, parity 0 patient with a known diagnosis of Poland syndrome were presented at her 30th weeks of gestation with shortness of breath. Her medical history was unremarkable other than Poland syndrome. Her physical examination was normal except absent pectoralis major muscle, short forearm, hypoplastic hand, brachysyndactyly, second-third finger hypoplasia, and atrophic breast on the right, components of her Poland syndrome diagnosis (Figure 1, 2). Also, minimally decreased respiratory sounds noticed on auscultation on the affected side. Complete blood count and routine laboratory evaluation were in normal range. Karyotype analysis and florescent *in situ* hybridization (FISH) for chromosome 11q were also normal. Obstetric ultrasonography and umbilical artery Doppler evaluation were normal. During her follow up examination in one week, she complained about worsening dyspnea. Patient was hospitalized for close observation and detailed evaluation. Respiratory function tests, pulse oximetry readings, arterial blood gas analysis, electrocardiography, non-stress test were normal. There was minimal anterior septum hypokinesis, and first degree pulmonary valve regurgitation on echocardiography. For a possible preterm delivery, antenatal maternal steroid administration was achieved by two doses of betamethasone 12 mg (Celestone Chronodose; Merck Sharp&Dohme, New Jersey, USA) via intramuscular route. Patient's respiratory complaints progressed further, being orthopneic at 32 weeks of gestation and decision to intervene by cesarean delivery was made. After delivery, patient's complaints dramatically resolved with no complication.

Figure 1. Right hand anomaly of the patient with Poland syndrome

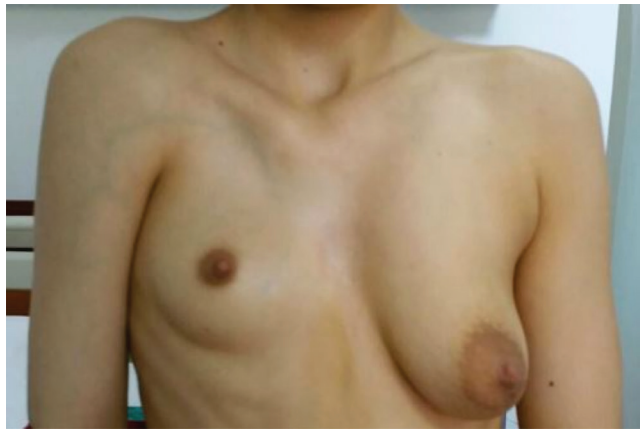

Figure 2. Unilateral right sided pectoralis major muscle agenesis and ipsilateral breast hypoplasia

Discussion

Etiology of Poland syndrome remains unknown. Subclavian artery disruption and abnormal perfusion related aplasia/hypoplasia of regional muscles and other tissues between 42-47 days of embryogenesis is common popular theory (4). However, this is challenged by a latest case report with intact thoraco-acromial arteries and muscle fascia, suggesting an alternative theory of paraxial mesenchyme developmental failure (5). Recently, monozygotic twins with this syndrome were found to have 11q12.3 deletion, pointing five candidate genes in the deleted region (6). The majority of Poland syndrome cases are sporadic however there are some familial clustered cases implying different inheritance patterns (7). Our case has normal karyotype and FISH result and she did not mention any relatives with similar findings. Majority of the surgical intervention reports cite cosmetic reasons for indication of surgery (2,8). Apart from scarce cases of lung herniation, recurrent pneumothorax and paradoxical respiratory movements, serious cardiac or pulmonary complaints have not been reported (3). In addition, no pregnant case reports could be spotted in

the PubMed search. Our case had a mild complaint of dyspnea in midtrimester and worsened progressively with advancing gestational age. Normal respiratory function tests, echocardiography and arterial blood gas analysis held us from earlier intervention even though patient's subjective complaint was impressive. Significant respiratory tract changes are expected during pregnancy. Functional residual capacity, residual volume, and expiratory reserve volume decreases. Diaphragm rises approximately 4 cm and thoracic cage girth increases 6 cm. In our case, with enlarging uterus, it is possible that elevation and limitation of diaphragm movement was more prominent and negatively affected stabilization of affected right hemithorax, caused significant respiratory discomfort. Even though we could not document respiratory dysfunction with tests, it seemed that we would see deteriorated test results if preterm delivery was held for longer. Our case presentation must alert clinical thinking in a way that even benign conditions like Poland syndrome may complicate pregnancy with their unexpected effect on normal pregnant physiologic adaptations. Poland syndrome can cause significant respiratory discomfort during pregnancy that may not be reflected on respiratory function tests and can alter obstetric management. Therefore, early baseline respiratory function tests may be indicated in pregnant patients with Poland syndrome in order to discern worsening results (even in the normal range) with advancing gestational age.

Ethics

Informed Consent: A written informed consent was obtained from patient for this presentation.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: E.Z., B.B., Concept: E.Z., S.D.S., Design: E.Z., Data Collection or Processing: B.B., Analysis or Interpretation: E.Z., S.N.A., Literature Search: E.Z., S.D.S., Writing: E.Z., S.N.A.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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Case Report / Olgu Sunumu

Can Allergen Specific Immunotherapy Induce Familial Mediterranean Fever Attacks?

Allerjen Spesifik İmmünoterapi Ailevi Akdeniz Ateşi Ataklarını Tetikleyebilir mi?

Songül Çildağ, Taşkın Şentürk, Gökhan Sargın

Adnan Menderes University Faculty of Medicine, Department of Immunology-Allergy, Aydın, Turkey

Abstract

Allergen-specific immunotherapy is a treatment aimed to reduce allergic symptoms and need for medication use after exposure to specific allergens. Allergen-specific immunotherapy is the only curative treatment that can change the natural course of allergic diseases. Although, allergen-specific immunotherapy is quite effective in the treatment of atopic dermatitis, allergic asthma, allergic rhinitis, and insect bites, serious treatment-related side effects may still occur. Since allergen-specific immunotherapy can cause changes in the immune system, it is theoretically possible that it can also affect immune system mediated inflammatory diseases such as autoimmune diseases. This is the first case report of an occurrence of Familial Mediterranean Fever attacks during allergen-specific immunotherapy.

Öz

Allerjen spesifik immünoterapi kişide spesifik allerjen maruziyeti sonrasında gelişebilecek allerjik semptomları ve ilaç kullanım ihtiyacını azaltmaya yönelik bir tedavi şeklidir. Atopik dermatit, allerjik astım, allerjik rinit ve böcek sokmalarında oldukça etkin bir tedavi şekli olmakla birlikte allerjen spesifik immünoterapi ile ilişkili ciddi yan etkiler de oluşabilmektedir. Allerjen spesifik immünoterapinin, immün sistem üzerinde yapmış olduğu değişiklikler nedeniyle, otoimmün hastalıklar gibi immün sistem aracılığı ile gelişen enflamatuvar hastalık oluşumunu da etkileyebileceği düşünülmektedir. Burada sunduğumuz olgu, allerjen spesifik immünoterapi tedavisi sırasında Ailesel Akdeniz Ateşi atağı semptomları gelişen, bildirilmiş ilk olgu sunumudur.

Keywords
Allergen-specific, immunotherapy, Familial Mediterranean Fever

Anahtar Kelimeler
Allerjen spesifik, immünoterapi, Ailesel Akdeniz Ateşi

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Address for Correspondence/Yazışma Adresi:
Songül Çildağ MD,
Adnan Menderes University Faculty of Medicine, Department of Immunology-Allergy, Aydın, Turkey
Phone : +90 506 509 27 53
E-mail : songulcildag@yahoo.com

ORCID ID: orcid.org/0000-0001-9617-0925

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Introduction

Allergen-specific immunotherapy (ASIT) is a treatment aimed to reduce allergic symptoms and need for medication use after exposure to specific allergens. The treatment is based on the principle of administration of increasing doses of the allergen. The ASIT has been used in the treatment of allergic diseases for more than a century, and it is the only curative treatment that can change the natural course of allergic diseases (1). The basic objective is to provide peripheral T cell tolerance. Peripheral T cell tolerance is achieved by induction of T

regulatory (Treg) cells that are capable of producing anti-inflammatory cytokines such as interleukin (IL)-10 and transforming growth factor (TGF)-β. Treg cells reduce the T helper (Th) 2 response, in addition to reducing dendritic cell, mast cell, basophil, and eosinophil responses. Moreover, while inducing the production of immunoglobulin (Ig) G4 and IgA, Treg cells regulate an allergen-specific IgE response (2-6). Although, ASIT is quite effective in the treatment of atopic dermatitis, allergic asthma, allergic rhinitis, and insect bites, serious treatment-related side effects may still occur. The ASIT related side effects are divided into two groups: local and systemic side effects. The local side effects include redness, itching and swelling at the injection site, while systemic side effects can range from a mild reaction to life threatening severe anaphylaxis (7,8). Information regarding the long-term side effects of treatment is scarce. Since ASIT can cause changes in the immune system, it is theoretically possible that it can also affect immune system mediated inflammatory diseases such as autoimmune diseases. Sjögren's syndrome, multiple sclerosis, localized scleroderma, recurrent pericarditis and vasculitis have all been reported to occur during ASIT. This present case is the first report of an occurrence of Familial Mediterranean Fever (FMF) attacks during ASIT.

Case Report

A 34-yr-old female patient was admitted to our clinic for continuation of her treatment. She had been treated for allergic rhinitis, using the grass pollen antigens group conventional immunotherapy treatment, for 3.5 years in another clinic. Based upon the patient's medical history, we learned that in the beginning the second year of her immunotherapy significant clinical response was achieved; the patient no longer required treatment with antihistamines. However, we learned that 4 months ago the patient was diagnosed with FMF. The patient reported no family history of FMF. Her complaints started 6-7 months ago, with once a month abdominal pain attacks lasting 3-4 days, accompanied by fever. Fever ranging from 38-39 degrees Celcius and there was diffuse abdominal pain. Abdominal attacks were not associated with menstruation. She had no contraceptive ring. The physician from the initial clinic that the patient presented to diagnosed her with FMF and initiated a 1.5 mg/day colchicine treatment. The colchicine treatment gave a dramatic response. Genetic testing did not detect any mutations consistent with FMF for E148Q, M680I, M694V, V726A, F479L, A744S, R761H. The patient's physical examination performed in our clinic was normal. Moreover, her complete blood count, sedimentation rate, C-reactive protein, liver function tests, kidney function tests, urinalysis, and anti-nuclear antibody levels were within the normal limits. The patient had been undergoing ASIT treatment for 3.5 years and experienced a significant improvement of her symptoms. The onset of FMF had started during this treatment period and since the patient did not have a family history FMF, we suggest that the FMF attacks may have been triggered by ASIT. For this reason, and also because the immunotherapy completed its 3.5-year course, we decided to terminate the patient's immunotherapy and closely follow-up the patient.

Discussion

Although short-term local and systemic side effects of ASIT are known, long-term side effects are not well known (9). There are publications that suggest that ASIT treatment could cause the development of autoimmune diseases. Sjögren's syndrome, multiple sclerosis, scleroderma, pericarditis and vasculitis are among such reported autoimmune diseases (9-13). However, no publications exist in the literature with regard to a link between ASIT applications the development FMF attacks. ASIT is the only curative treatment for allergic diseases. It causes the induction of allergen-specific Treg cells that produce IL-10 and TGF-β. This induction results in a B cell increase in the production of IgG 4 and IgA, with a decrease in the production IgE. The ASIT stimulates immunosuppressive Treg cells and shifts the Th1-Th2 balance towards Th1 by partially increasing the activity of suppressor T lymphocytes. It was determined that while the secretion of cytokines such as IL-4, IL-5, IL-9, IL-13, tumor necrosis factor (TNF)-α and IL-1 from Th2 cells decreases, the synthesis of cytokines such as IL-2, IL-12, IL-18, IFN-γ and TNF-β by Th1 increases, therefore changing the cytokine profile of T cells. In addition, the production of TGF-β, as a result of Treg cell induction, increases the differentiation of Th17, which is thought to be associated with autoimmune diseases (11,14-16). FMF is a disease characterized

by abdominal pain, chest pain or joint pain caused by inflammation in one or several of the following: peritoneum, pleura or synovial serous membranes. The course of FMF attacks is accompanied by fever. The attacks are self-limiting, lasting for 1-3 days, and heal spontaneously if left untreated. In 70% of the patients, symptoms appear in the first decade of life, while in 90% of them they are observed in the first two decades of life (17-19). FMF is a common disease in communities originating from the Eastern Mediterranean, particularly Jews, Turks, Armenians and Arabs. However, the disease has been diagnosed even in Japanese patients (20). The carrier frequency in Turkish, Armenian and Jewish populations were detected at high levels such as 1/3-1/5 (21,22). The disease-causing gene (*MEFV*) encodes for a protein called pyrin also known as marenostrin (Marenostrum: Mediterranean). In healthy individuals, under normal conditions, pyrin plays a role in controlling inflammation. Mutations in this gene may result in the inability of pyrin to perform its function, thus leading to deterioration of the control of inflammation (23,24). The inflammatory response caused by minor trauma in the joints and by stress, which is induced by variety of cytokines, are inhibited in the presence of normal pyrin, however in patients with FMF it is thought that mutant pyrin is not able to control the inflammatory response (25). Wide expression of pyrin in mature neutrophils suggests that this protein may provide down regulation of the inflammation mediators (26,27). Since neutrophils are the main cells of the acute inflammatory process, mutated pyrin's inability to perform its function may lead to the uncontrolled activation of neutrophils and cause the migration of these cells to serosal tissue (28). The emergence of attacks due to stress, the onset of attacks with metaraminol infusion and the response to colchicine treatment suggest that a defect in the metabolism of catecholamines may be involved in the pathogenesis of FMF (29). Today, the most widely accepted opinion on the pathogenesis of the disease is that a deficiency of C5a inhibitor, which is an inhibitor quite strong granulocyte chemoattractant C5a, may cause an acute inflammatory attack (30). It is also thought that the presence of pyrin increases the synthesis of C5a/IL-8 inhibitory factor, while in patients with FMF the C5a/IL-8 inhibitory factors are deficient (31). There was no *MEFV* mutation and no family history of FMF in our patient, which suggests a sporadic case of FMF. Since the patient's symptoms manifested silently, we hypothesize that the FMF attacks developed due to the changing immune response as a result of ASIT treatment. In addition, the patient was asymptomatic for allergic rhinitis; therefore, we terminated the patient's treatment. One reason that ASIT treatment may trigger FMF attacks is by inciting a shifting in the direction of Th1/Th2 balance towards the Th1, with a subsequent increase in the serum IL-17 levels, which has an important role in the etiopathogenesis of autoimmune diseases. In patients with FMF, serum IL-17 levels were high both during the attack one of the autoinflammatory disease periods and during asymptomatic periods (32). During FMF attacks, IL-17 plays an important role in the activation of neutrophils, predominant cells at the serosal surfaces. In addition, it stimulates the maturation, migration and function of neutrophils. Moreover, IL-17 ensures the migration of neutrophils to the peritoneal cavity during the attack period (33,34). In our case, we think that the increase of IL-17 levels induced by the ASIT treatment may have triggered the FMF attacks. But we did not find any data on this subject in the literature. So, we think that this issue should be investigated.

Ethics

Informed Consent: Informed constent was not taken because there was no information sharing involving personal data.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: S.Ç., T.Ş., Concept: S.Ç., T.Ş., G.S., Design: S.Ç., T.Ş., G.S., Data Collection or Processing: S.Ç., T.Ş., G.S., Analysis or Interpretation: S.Ç., T.Ş., G.S., Literature Search: S.Ç., T.Ş., G.S., Writing: S.Ç., T.Ş., G.S.

Conflict of Interest: No conflict of interest was declared by the authors.

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Case Report / Olgu Sunumu

Maxillary Fibrous Dysplasia with Cone Beam Computed Tomography Findings: A Case Report

Konik Işınlı Bilgisayarlı Tomografi Bulguları Olan Maksiller Fibröz Displazi: Bir Olgu Sunumu

Gülsün Akay[1], Kahraman Güngör[2]

[1]Tepebaşı Oral and Tooth Health Training and Research Hospital, Clinic of Oral and Dentomaxillofacial Radiology, Ankara, Turkey
[2]Gazi University Faculty of Dentistry, Department of Oral and Dentomaxillofacial Radiology, Ankara, Turkey

Abstract

Fibrous dysplasia (FD) is a slowly growing benign skeletal fibro-osseous condition, resulting from a localized change in normal bone metabolism that results in the replacement of all the components of cancellous bone by fibrous tissue. A 50-yr-old male patient with FD attended our clinic with a complaint of swelling in the right maxilla. In extra-oral examination, a significant asymmetry was observed. Intraoral examination revealed a painless swelling at the right maxillary posterior region. Increase in bone formation within the lesion was observed with a radiographic appearance that is referred to as "ground glass". The aim of this case report was to present clinical, histopathological and radiographic findings of a patient with FD.

Öz

Fibröz displazi (FD) kemiğin iyi huylu yavaş gelişen bir fibro-osseöz lezyonudur. Normal kemik metabolizmasındaki değişimin sonucu kansellöz kemiğin tüm içeriğinin fibröz dokuyla yer değiştirmesi sonucu gelişir. Elli yaşındaki erkek hasta sağ maksilladaki ağrısız şişlik yakınması ile kliniğimize başvurdu. Ekstraoral muayenede asimetri gözlenen hastanın intraoral muayenesinde sağ maksilla posterior bölgede ağrısız bir şişlik belirlendi. Kemik yapımındaki artış ile birlikte "buzlu cam" olarak adlandırılan radyografik görüntü gözlendi. Bu olgu sunumunun amacı FD tanısı konulan bir hastanın klinik, histopatolojik ve radyografik bulgularını sunmaktır.

Keywords
Fibrous dysplasia, cone beam computed tomography, ground glass, panoramic radiography

Anahtar Kelimeler
Fibröz displazi, konik ışınlı bilgisayarlı tomografi, buzlu cam, panoramik radyografi

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Address for Correspondence/Yazışma Adresi:
Gülsün Akay MD, Tepebaşı Oral and Tooth Health Training and Research Hospital, Clinic of Oral and Dentomaxillofacial Radiology, Ankara, Turkey
Phone : +90 535 981 39 86
E-mail : akay.gulsun@hotmail.com
ORCID ID: orcid.org/0000-0002-1767-1383

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Introduction

Fibrous dysplasia is a benign, fibro-osseous lesion of the bone that results from a localized change in normal bone metabolism. This disease usually exhibits as an asymptomatic, slow enlargement of the affected bone (1). The etiology of the disease is still unclear, but several factors play role. The molecular etiology has been linked with a mutation in the Gs-α gene, affecting proliferation and differentiation of fibroblasts/osteoblasts, which is coded by the *GNAS1* gene (guanine nucleotide-binding protein, a stimulating activity polypeptide) (1-3).

Fibrous dysplasia may affect a single bone or multiple bones (4). The most common bones of fibrous dysplasia are the ribs, femur, tibia, maxilla and mandible (5). The mainly forms of fibrous dysplasia are monostotic form (70-80% of cases) with one bone involvement and polyostotic form with several bones involvement (6,7). Polyostotic fibrous dysplasia may be associated with Mc-Cune Albright syndrome and Jaffe-Lichtenstein syndrome. Mc-Cune Albright syndrome includes polyostotic fibrous dysplasia, multiple endocrine disorder such as precocious puberty or hyperthyroidism and cafe´-au-lait pigmentation on the skin. Jaffe-Lichtenstein syndrome is characterized by multiple bone lesions involvement of fibrous dysplasia and irregular skin pigmentations (café-au-lait spots) (1,2). Mazabraud syndrome is another rare disorder associated with polyostotic fibrous dysplasia, in which fibrous dysplasia is combined with intramuscular myxomas (2). Craniofacial fibrous dysplasia is a form of fibrous dysplasia affecting the cranial base, involves two or more bones of the maxillofacial region and often includes the maxilla, zygoma, sphenoid, temporal bone, fronto-nasal bones and base of the skull (8,9). The monostotic form is usually diagnosed after puberty, patients in the second-third decades can also be asymptomatic, whereas polyostotic form is usually diagnosed before puberty. The monostotic form affects both genders equally, but female predilection has been reported in the polyostotic form (9,10). The aim of this reported is to evaluate clinical, histopathological and radiographic findings of a patient with monostotic fibrous dysplasia.

Case Report

A 50-yr-old Caucasian man patient was referred to oral and dentomaxillofacial radiology clinic with a chief complaint of unilateral painless swelling of the right maxillary posterior region. It was learned that tooth extraction done years ago because of dental caries. He stated that swelling had occurred in the same area 8 or 10 years ago and had been removed by surgical approach. His medical history was unremarkable, and the neurological examination was normal. In clinical examination, swelling was observed at the right maxillary posterior region and lesion caused painless palatine-vestibule expansion (Figure 1). The overlying mucosa was in normal appearance. In panoramic radiographic examination, partially edentulous maxilla

Figure 1. Intraoral photographs, swelling at the right maxillary posterior region of the patient

is noted on this radiograph with missing right maxillary molars. Teeth had been extracted a long time ago. Diffuse “ground glass” appearance was observed at the right maxillary edentulous region (Figure 2). Then, the patient was referred for the cone-beam computed tomography (CBCT) examination to determine the localization and structure of the lesions. An informed consent was obtained from patient. The CBCT image was obtained using a Promax 3D unit (Planmeca, Helsinki, Finland), operating at 90 kVp, 14 mA, with a 0.16 mm voxel size, exposure time of 6 seconds and a field of view of 8 cm. A high-density area was noted extending from tuberculum molare to the right first premolar region, which leads to significant expansion of the right maxillary bone, maxillary sinus walls, intramedullary area and cortical thinning. CBCT images showed that lesion occupied significant portion of the maxillary sinus (Figure 3). It measured about 5x3x5 cm anteroposterior, buccopalatal, and superoinferior dimensions, respectively. Based on clinical and radiographic findings, a diagnosis of fibrous dysplasia in the patient was revealed.

Incisional biopsy of the lesion was performed under local anesthesia and was sent for histopathological examination to pathology department for definitive diagnosis. Histological examination of the bone: irregularly shaped trabecular was viewed within

cellular fibrous stroma, composed of fibroblastic spindle cells. Planned treatment for the patient was a contour excision of the right maxillary region for prosthetic rehabilitation. He was called for control at regular intervals.

Discussion

Fibrous dysplasia is a significant lesion affecting the maxillofacial region because it can cause severe facial deformity, asymmetry (11). Craniofacial region is involved in 25% of the fibrous dysplasia cases. The maxilla and mandible are the most frequently affected bones in the craniofacial region (7). The maxilla is affected more often than the mandible and it develops more generally in the posterior region. Most of the lesions are unilateral (2,5). Maxillary lesions may expand to maxillary sinus, zygoma, sphenoid bone and floor of the orbit. The form with involvement of several adjacent bones, such as sphenoid, zygoma, fronto-nasal bones and base of the skull, has been called as craniofacial fibrous dysplasia (10). Craniofacial fibrous dysplasia can cause severe facial deformity and asymmetry, and may lead to neurological symptoms such as hypertelorism, visual impairment and blindness by involving the orbital and periorbital bones (7). Maxillary lesions may extend into maxillary sinus and usually occur in the lateral wall, and the last section of the sinus to be involved is usually the most posterosuperior portion. Also, the peripheral border of the lesion appears as parallel thickening normal shape of the antrum (5). Obliteration of the maxillary sinus is a common finding (2). In this case, observed existing painless swelling in the right maxillary posterior region partially occupied the maxillary sinus. We diagnosed as monostatic type which affected no other bones in the maxillofacial region. The diagnosis of fibrous dysplasia is based on results of the clinical, radiological and histopathological features. The radiological appearance of fibrous dysplasia shows various appearances according to the degree of maturation and quantity of bony matrix within the lesion. In the earlier stages, the lesion may be more radiolucent and well-defined (5). As the disease progresses, it becomes mottled and more radiopaque. The distinct radiopaque patterns are described such as peau d' orange appearance, resembling the surface of an orange, granular or ground glass appearance, resembling the small fragments of a shattered windshield, wispy cotton wool like appearance, or amorphous dense pattern (5). Also, fingerprint appearance is defined as trabeculae aligned concentrically, similar to a fingerprint (12). Fibrous dysplasia commonly altered the lamina dura to the surrounding abnormal bone pattern, narrowing of periodontal ligament space is a useful diagnostic feature for this disease (12). CBCT can be useful in assessing expansion, cortical borders, and lesion's internal structure (5). There are three different image characteristics on CT findings. The most common appearance of fibrous dysplasia is a ground glass appearance (56%), the others homogeneously dense pattern (23%), and cystic variety (21%) (8). In our case, CBCT images showed expansive mass at ground-glass appearance with maxillary sinus expansion. Certain diagnosis of fibrous dysplasia is made by histopathological examination. The macroscopic appearance is in the form of a white and brown solid mass expanding the medullary cavity of the bone (7). The histopathological features show benign fibroblastic tissue, arranged in a loose, and irregular, curvilinear

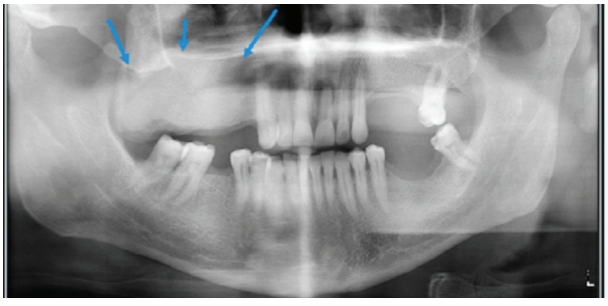

Figure 2. Panoramic radiograph, diffuse granular appearance known as a "ground glass" appearance and expansion

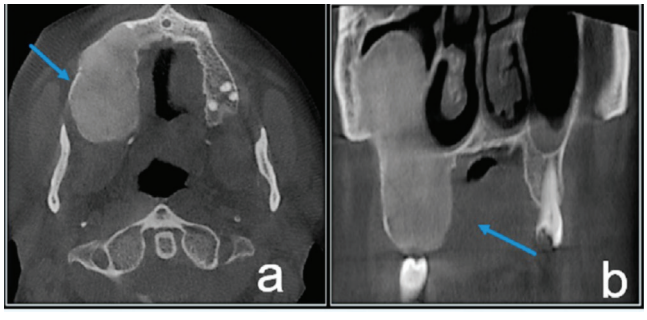

Figure 3. Cone-beam computed tomography images of the maxilla, showing a high-density area, extending from tuberculum molare to the right canine region, the outer cortical plates have been thinned a) axial, shows lesion occupied significant portion of the maxillary sinus, b) coronal planes

trabeculae of woven bone with little evidence of osteoblast in fibrous tissue. The bony trabeculae show an abnormal arrangement, vary in shape and some are thin and C-shaped, called as "Chinese" characters trabecular (2,10). Patients with jaw involvement first may complain facial asymmetry or an enlarging deformity of the alveolar process and pain is rare (5). Although patients are usually asymptomatic, patient's age at the time of diagnosis, characteristics of pain, and process of rapid enlargement of the lesion are important points of the history. It is not accepted that biopsy or surgery is necessary for asymptomatic fibrous dysplasia, but routine follow-up of these patients should be performed (13). Radiotherapy is not recommended, because it may induce malignant transformation (8). In our case, surgical approach was carried out for prosthetic reason and the patient was called for controls with regular intervals. It must be differentiated from other diseases with a similar radiographic appearance, including central giant cell tumor, Paget disease, ossifying fibroma, giant cell reparative, granuloma, brown tumor, eosinophilic granuloma, hemangioma, and well-differentiated osteosarcoma (13). The differentiation from ossifying fibroma can be the most difficult, but ossifying fibroma is an expansive lesion with a smooth margin and has tumorlike behavior. Paget's disease influences older age groups, not unilateral like fibrous dysplasia (5,8).

MacDonald-Jankowski (11) reported as 18% recurrence rate after treatment. In our case, we learned that the lesion had already developed in the same region and that a surgical procedure had been performed, do not have enough information about the size of the previous lesion. However, we think that the lesion was recur or reactive. Malignant transformation is rare, and malignancy has been described in <1% of the cases (4). Lesions may recur or progress to more serious results such as sarcoma (11). Follow-up and recurrence are usually inter-related. Long term periodic follow-up is recommended to determine recurrence and malignant changes (10).

Fibrous dysplasia is a benign disease that has the potential to cause significant cosmetic and functional disturbance. The awareness of dentists about clinical and radiographic findings of fibrous dysplasia is important for early diagnosis. Particularly, CBCT plays an important role in the diagnosis of fibrous dysplasia.

Ethics

Informed Consent: It was taken.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Medical Practices: G.A., K.G., Concept: K.G., G.A., Design: K.G., Data Collection or Processing: G.A., Analysis or Interpretation: K.G., G.A., Literature Search: G.A., Writing: G.A., K.G.

Conflict of Interest: No conflict of interest was declared by the authors.

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