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Supratentorial Metastasis of Glioblastome Multiforme to the Pituitary Stalk

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LEFT ATRIAL APPENDAGE STUNNING AFTER ELECTRICAL CARDIOVERSION IN PATIENTS WITH ATRIAL FLUTTER AND FIBRILLATION

İrem Dinçer* • Ömer Akyürek* • Tamer Sayın* • Sadi Güleç*
F. Sinan Ertaş* • Eralp Tutar* Çetin Erol* • Derviş Oral*

SUMMARY

Background: *Left atrial (LA) and left atrial appendage (LAA) stunning after cardioversion (CV) has been proposed as the responsible phenomenon in the etiology of postcardioversion thromboembolic events. Although LA and LAA stunning have been observed after conversion of atrial fibrillation (AF) and atrial flutter (AFL) to sinus rhythm, there is still controversy about the degree of stunning and the need for anticoagulation after CV of AFL.*

Hypothesis: *Recent reports suggest that in the absence of effective anticoagulation, incidence of thromboembolic events following CV of AF is high. Consequently, we hypothesize that the degree of LAA stunning following CV of AFL may be equally as remarkable.*

Methods: *A group of 40 patients with either AFL (n=19) or AF (n=21) were assessed for spontaneous echo contrast (SEC) and thrombus formation and LAA emptying velocities were measured immediately before and after CV. LA function was evaluated by measuring mitral inflow A-wave velocities with pulse wave Doppler in both groups following CV.*

Results: *LAA emptying velocities were higher in AFL patients than in AF patients before CV (0.58±0.27 m/sec for AFL and 0.32±0.11 m/sec for AF p=0.02). LAA emptying velocities decreased significantly in both groups of patients after CV. (0.58±0.27 m/sec to 0.25±0.11 m/sec p=0.001 for AFL and 0.32±0.11 m/sec to 0.22±0.4 m/sec p=0.007 for AF). However, the degree of impairment in LAA function after CV was more pronounced in patients with AFL (p=0.02). Increased SEC occurred in eight out of 19 patients (42%) with AFL and only seven out of 21 patients (33%) with AF after CV (p=NS). Doppler data showed three patients (15%) in the AFL group and five patients (21%) in the AF group had no identifiable atrial activity immediately after restoration of sinus rhythm. Mitral inflow A-wave velocities were greater in patients with AFL than in those with AF (p=0.01) immediately after CV.*

Conclusion: *LAA stunning after CV occurs in patients with AF and AFL, but is more pronounced in patients with AFL. However, LA contractility, although impaired, is better preserved in patients with AFL.*

Key Words: *Atrial flutter, cardioversion, transesophageal echocardiography, left atrial appendage function*

ÖZET

Atrial Flutter ve Fibrilasyonu Olan Hastalarda Elektrikikardiyoversiyon Sonrası Sol Atrial Appendiks Stunningi

Amaç: *Sol atrium (LA) ve appendikste (LAA) kardiyoversiyon (KV) sonrası oluşan sersemleme bu dönemde oluşan tromboemblik olayların sorumlusu olarak gösterilmektedir. Atrial fibrilasyon (AF) ve flutterli (AFL) hastalarda kardiyoversiyon sonrası sol atrium ve appendiskte oluşan sersemleme daha önceki çalışmalarda gösterilse de, atrial flutterli hastalarda oluşan sersemlemenin derecesi ve antikuagülan tedavi kullanımı halen tartışmalıdır.*

Metod: *Çalışmaya AF (n=21) ve AFL tanısı olan 40 hasta alındı. Kardiyo versiyondan hemen önce ve sonra sol atrial appendiksteki spontan eko kontrast (SEK) ve trombüs oluşumu ile sol atrial appendiks boşalma hızları ölçüldü. Kardiyoversiyon sonrası sol atrium fonksiyonlarını değerlendirmek amacı ile*

Bulgular: *Kardiyoversiyon öncesi LAA boşalma hızları AFL'lı hastalarda daha yüksekti (AFL'lı hastalarda 0.58±0.27 m/sn ve AF'lu hastalarda 0.32±0.11 m/sn p=0.02). Kardiyoversiyon sonrası her iki hasta grubunda da LAA boşalma hızları belirgin olarak azaldı (AF'lu hastalarda 0.32±0.11 m/sn'den 0.22±0.4 m/sn p=0.007, AFL'lı hastalarda 0.58±0.27 m/sn'den 0.25±0.11 m/sn p=0.001). Bununla beraber AFL'lı hastalarda LAA fonksiyonlarında bozulma AF'lu hastalardan daha belirgindi (p=0.02). Kardiyoversiyon sonrası AF'lu hastaların 7'sinde (%33) SEK artış gözlenirken AFL'lı hastaların 8'inde (%42) artış oldu (p=NS). Sinüs ritmini sağlanmasından hemen sonra mitral akım örneklerinde AF' olan hastaların 5'inde (%21), AFL hastalarında 3'ünde (%15) sol atrium appendiks aktivitesini gösteren A dalgası gözlenmedi. Mitral akım A dalga hızları AFL hastalarda AF'lu hastalara oranla daha yüksekti (p=0.01).*

Sonuç: *Kardiyoversiyon sonrası AF ve AFL'li hastalarda sersemleme oluşmakta bu AFL hastalarda daha belirgin olarak gözlenmektedir. Bununla beraber LA aktivitesi kardiyoversiyon sonrası bozulmasına rağmen AFL hastalarda AF'lu hastalara oranla daha iyi korunmaktadır.*

Anahtar Kelimeler: *Atrial flutter, kardiyoversiyon, transösefageal ekokardiyografi, sol atrial appendiks fonksiyonları*

* Cardiology Department of Ankara University Medical School

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Transient mechanical dysfunction of the left atrium (LA) and left atrial appendage (LAA), or "stunning", is well-demonstrated in patients with atrial fibrillation (AF) undergoing cardioversion (CV)(1-4). Recent studies showed that LA and LAA stunning also occurs in patients undergoing CV of atrial flutter (AFL) (5-7). There is only one study comparing the degree of LA and LAA stunning after CV of AF and AFL (5). On the basis of previous data demonstrating a high incidence of thoromboembolic events in patients with AFL undergoing CV in the absence of effective anticoagulation (8-12), we hypothesized that LAA stunning after CV of AFL would be as remarkable as after CV of AF. To test this hypothesis, we evaluated LAA stunning after CV of AF and AFL and compared the degree of impairment in LAA function in both groups. We also measured mitral inflow A-wave velocities to determine the LA contractile function immediately after CV.

METHODS

Fifty-three 53 patients admitted consecutively to our institution for cardioversion of AF (n=33) and AFL (n=20) with arrhythmia duration of more than two days were considered for this study. All patients gave their written informed consent to participate. The duration of arrhythmia was estimated by asking about the onset of symptoms, or, in asymptomatic patients, by using the latest available electrocardiography.

Of the 53 patients considered for participation, data from 13 patients was excluded from further analysis due to LAA thrombus (four patients, all in the AF group) or unsuccessful CV (eight in the AF group and one in the AFL group), reducing the study population to 40 patients (AF=21 patients, AFL=19 patients).

All patients were receiving effective anticoagulation therapy, either with warfarine or heparin.

Transthorasic echocardiography (TTE) was performed using a Hewlett Packard Sonos 5500 and a 2.5 MHz probe. Transesophageal echocardiography (TEE) was performed with the same device using a 5 MHz multiplane probe. All patients received a topical anesthesia of 10% Xylocaine and were sedated with 0.07-0.1 mg/kg midazolam before TEE. After complete TEE examination, LAA emptying velocities were obtained by positioning the sample volume at the entrance of the LAA at the point of lowest wall motion noise and most optimal alignment of the ultrasonic beam to flow. Calculations were made off-line by averaging 10 cycles in patients with AF and six cycles in patients with AFL. LA and LAA were examined for the presence of SEC, defined as dynamic intracavitary echoes with a characteristic swirling pattern (13), and for the presence of thrombus, defined as a uniform echo-dense mass distinct from the atrial wall. Gain settings were adjusted to minimize gray noise artifacts, and the severity of SEC was graded online independently by two observers, according to the following criteria: (13) Grade 0 - absence of any echogenicity; Grade 1 - minimal echogenicity located in LAA or sparsely distributed in the main cavity of LA, detectable during cardiac cycle only, imperceptible at operating gain settings for two-dimensional echocardiographic analysis; Grade 2 - denser swirling pattern than Grade 1, but with similar distribution, detected without gain settings; Grade 3 - dense swirling pattern in LAA, generally associated with somewhat lesser intensity in the main cavity, may fluctuate in intensity, but detectable constantly throughout the cardiac cycle; Grade 4 - intense echo density and very slow swirling patterns in LAA, usually with similar density in the main cavity. Before CV, additional sedation was provided using midazolam, as needed. CV was performed using a Hewlett Packard Cord master machine with an initial delivered energy of 200J for AF patients and 50J for AFL patients. After conversion to sinus rhythm and assumption of cardiopulmonary stability, the TEE probe was reinserted and LAA velocity profiles, SEC and thrombus formation were re-recorded in all patients. LA mechanical function was assessed by measuring mitral A-wave velocities with TTE from an apical four-chamber view, placing the pulse wave Doppler sample volume at the tips of the mitral valve leaflets. LAA emptying velocities and mitral inflow A-wave velocities were calculated by averaging three cardiac cycles in sinus rhythm. TTE and TEE examinations were completed within 15 minutes after CV in all patients. On completion of echocardiographic examination, each patient was monitored until recovery from sedation and observed in hospital until the following morning.

RESULTS

Clinical and echocardiographic variables of patients are summarized in Table 1. There were no differences with regard to age or gender between the two groups. The suspected etiologies of arrhythmias were

Table 1. Clinical and echocardiographic variables of patients

	All	Atrial Fibrillation	Atrial flutter	p=
Number of patients	40	21	19	NS
Men/Women	28/12	15/6	13/6	NS
Age(year)	55±8	58±11	51±7	NS
Underlying heart disease				NS
DCMP	11	5	6	
IHD	21	10	11	
HT	5	3	2	
Lone	3	3	0	
AF/AFL Duration				
(month)	4.7±5.3	5.6±4.3	4.2±3.1	0.04
LVEDD(cm)	5.9±0.6	5.8±0.5	6.0±0.6	NS
LVESD(cm)	4.2±1.1	4.1±0.6	4.2±1.3	NS
FS (%)	30±11	31.6±5	27.7±12	NS
LA(cm)	4.9±0.4	5.1±0.3	s4.7±0.4	NS

DCMP: Primer dilated cardiomyopathy, IHD. Ischemic heart disease, HT: Hypertension, AF: Atrial fibrillation, AFL: Atrial flutter, LVEDD: Left ventricle end diastolic diameter, LVESD: Left ventricle end systolic diameter, FS: Fractional shortening, LA : Left atrium

dilated cardiomyopathy, ischemic heart disease and hypertension, except for three patients in the AF group with AF only. Left ventricular diameters, fractional shortening and LA diameters were similar in both groups. The duration of arrythmia was longer in the AF group (p=0.04).

During a one-week follow-up period, there were no thromboembolic events. Recurrence of arrhythmia was observed in four patients in the AF group (19%) but none in the AFL group.

LAA emptying velocities and SEC before and immediately after CV (Table 2): LAA emptying velocities were higher in patients with AFL (p=0.02). After CV, LAA emptying velocities decreased significantly in both groups (p=0.007 for AF and p=0.001 for AFL). The degree of impairment was found to be more pronounced in patients with AFL (p=0.02) (Figure1).

Before CV, SEC was observed in 14 patients with AF (66%) and 11 patients with AFL (57%). After CV, an increase in SEC was observed in seven patients with AF (33%) and eight patients (42%) with AFL.

Mitral inflow A-wave velocities after CV: After conversion to sinus rhythm there was no identifiable atrial activity in five patients with AF (21%) and in three patients with AFL (15%). Immediately after CV, mitral inflow A-wave velocities were higher in patients with AFL than in those with AF (0.24±0.13 m/sec and 0.13±0.07m/sec respectively, p=0.01).

STATISTICS

Data is presented as mean ±SD. Intergroup comparisons of discrete variables were performed using Student's t test and comparisons of cathegoric variables using frequency tables and chi-square analysis. Results with a p value < 0.05 were considered as significant.

DISCUSSION

The major finding of our study is that LAA stunning after CV of AFL is more pronounced than after CV of AF. However, patients with AFL had better atrial contractility after CV.

Tabel 2. Left atrial appendage emptying velocity profiles before and after cardioversion and degree of impairment

	Atrial fibrillation	Atrial Flutter	p=
LAA emptying velocities (m/sec)			
Before CV	0.32±0.11	0.58±0.27	0.02
After CV	0.22±0.4	0.25±0.11	0.4
Degree of impairment (m/sec)	0.10±0.1	0.33±0.02	0.01
Worsening of SEC	33%	42%	NS

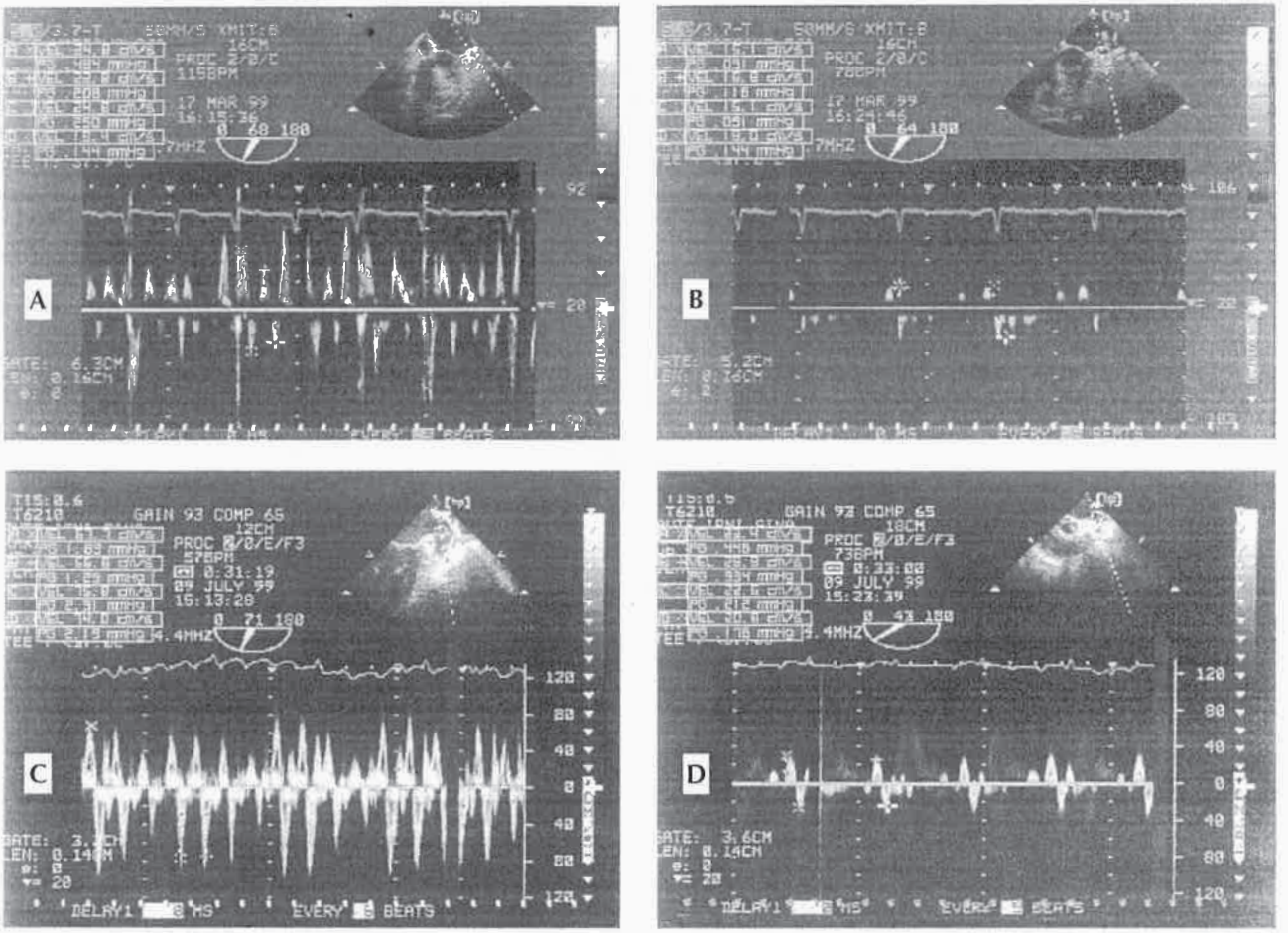

Figure 1: Left atrial appendage emptying velocities before and after cardioversion of atrial fibrillation (A-B) and atrial flutter (C-D).

The few studies that have examined LAA stunning immediately after CV of AFL have obtained different results regarding the degree of stunning, LAA emptying velocities and new development or worsening of SEC immediately after CV (5-7). Decrease of emptying velocities after CV has been reported to be between 26-66%, emptying velocities between 18.0±7.1 cm/sec to 40±25 cm/sec and new development or worsening of SEC between 21-80%. Our current study found a 57% decrease in emptying velocity (from 58±27 cm/sec to 25±11 cm/sec) and a worsening of SEC in 42% of patients. These differences in LAA function impairment may be connected to the length of arrhythmia, since the worst results were reported in connection with the longest duration of AFL (7).

There has been only one study comparing LAA stunning after CV of AF and of AFL (5). When the magnitude of stunning was compared, that study found no difference between the groups in the decrease in appendage emptying velocities; however, the emptying velocities were greater in AFL patients before CV and remained higher after CV. In contrast, our study found the magnitude of LAA appendage stunning to be more pronounced in patients with AFL than AF and found no difference between the groups in LAA emptying velocities after conversion to sinus rhythm. Our data does not allow for any conclusions as to the cause of the difference between the two groups in the degree of LAA stunning after CV.

LA mechanical dysfunction after CV of AF and AFL has been repeatedly demonstrated. We noted that transmitral A-wave velocity immediately after CV was significantly better in patients with AFL than in those with AF. This finding may seem unexpected, since LAA stunning is more pronounced in patients with AFL than in patients with AF. However, the degree of stunning in LA and LAA patients may not necessarily be the same, as demonstrated by an experimental

study that indicated more profound mechanical stunning in LAA (14).

Conclusion : The risk of thromboembolic events after CV of AFL in the absence of effective anticoagulation is reported to be up to 15% (12). Our data suggests that LAA emptying velocities are higher in AFL patients, but decrease more than those of AF patients after conversion to sinus rhythm. Accordingly, we support anticoagulation therapy as part of the treatment of AFL patients during the postcardioversion period. The duration of anticoagulation therapy after CV may be clarified through further studies.

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DÜZETLME

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CONGENITAL COMPLETE DEFICIENCY OF GH, TSH, AND PRL IN TWO SIBLINGS adlı yazının yazarları, içindekiler sayfasında yanlış yazılmıştır. Doğrusu ***"İffet Bircan, Serap Semiz, Sema Akçurin"*** olacaktır.

Düzeltir, özür dileriz.

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EVALUATION OF LEFT VENTRICULAR DIASTOLIC FUNCTION IN PATIENTS WITH RHEUMATOID ARTHRITIS USING ECHOCARDIOGRAPHY AND RADIONUCLIDE VENTRICULOGRAPHY

Serpil Savaş* • Özlem Küçük* • Şenay Kahramanlar*
Erkan İbiş* • Safiye Tuncer* • Çetin Erol* • Güneş Akgün*

SUMMARY

Excessive mortality from cardiovascular diseases, particularly congestive heart disease, has been reported in patients with Rheumatoid Arthritis (RA). The aim of this study was to determine the left ventricular diastolic function in patients with RA without clinically evident cardiovascular disease by using echocardiography and radionuclide ventriculography and to compare the results of both techniques in detecting subclinical cardiomyopathy.

Twenty-one patients (mean age 49.9 ± 13 yr., range 33-73; 18 female, 3 male) and 20 sex- and age-matched healthy controls (mean age: 44.4 ± 7.7 yr., range 37-68, 18 female, 2 male) were included in the study. Left ventricular diastolic function was evaluated using PW Doppler echocardiography and radionuclide ventriculography.

No echocardiographic abnormalities were detected in either group. In radionuclide ventriculography peak filling rates (2.7± 0.5 edc/sec vs 3.2 ± 0.2 edc/sec) and time to peak filling rates (169.6± 48.2 msec vs 126.4± 44.4 msec) were significantly more abnormal in patients with RA than in controls ($p<0.05$).

We conclude that RA is associated with asymptomatic left ventricular diastolic dysfunction, which may be a sign of subclinical myocardiopathy. Radionuclide ventriculography may be more valuable than echocardiography in assessing left ventricular diastolic function in patients with RA.

Key Words: *Rheumatoid Arthritis, heart, diastolic function, echocardiography, radionuclide ventriculography*

ÖZET

Romatoid Artrit'li Hastaların Sol Ventrikül Diyastolik Fonksiyonlarının Ekokardiyografi ve Radyonüklid Ventrikülografi ile İncelenmesi

Romatoid Artrit'li (RA) hastalarda özellikle konjestif kalp hastalığına bağlı olarak kardiyovasküler mortalite artışı olduğu bildirilmiştir. Bu çalışmanın amacı klinik olarak kardiyovasküler hastalığı olmayan RA'lı hastalarda ekokardiyografi ve radyonüklid ventrikülografi yöntemleri ile sol ventrikül diastolik fonksiyonunu belirlemek ve subklinik kardiyomiyopatiyi göstermede bu iki yöntemin sonuçlarını karşılaştırmaktır.

Yirmibir RA'lı hasta (ort. yaş 49.9±13 yıl, 33-73; 18 kadın ve 3 erkek) ve 20 yaş ve cinsiyeti uyumlu sağlıklı kontrol hasta (ort. yaş 44.4 ± 7.7 yıl, 37-68; 18 kadın ve 2 erkek) çalışmaya alındı. Sol ventrikül diastolik fonksiyonu PW Doppler ekokardiyografi ve radyonüklid ventrikülografi kullanılarak değerlendirildi.

Her iki grupta da ekoardiyografik bir patoloji saptanmadı. RA'li hastalarda radyonüklid ventrikülografi pik dolum hızları (2.7±0.5 edc/sec ve 3.2±0.2 edc/sec) ve pik dolum hızına ulaşma zamanı (169.6±48.2 msec ve 126.4±44.4 msec) kontrol grubuna göre anlamlı derecede farklı bulundu.

Sonuç olarak RA'te subklinik myokardiyopatin bir bulgusu olarak asemptomatik sol ventrikül diastolik disfonksiyonu görülebilir. Sol ventrikül diastolik fonksiyonun radyonüklid ventrikülografi ile saptanması ekokardiyografik yönteme göre daha değerlidir.

Anahtar Kelimeler: *Romatoid Artrit, kalp, diastolik fonksiyon, ekokardiyografi, radyonüklid ventrikülografi*

It has long been known that Rheumatoid Arthritis (RA) is associated with a variety of cardiac manifestations such as pericarditis (1), valvular disease (2), myocardial involvement (3), coronary vasculitis (4) and ventricular arrhythmias (5,6). In recent years, excessive mortality from cardiovascular diseases, particularly from congestive heart failure, has been reported (7,8,9). There are several echocardiographic studies that show left ventricular diastolic dysfunction in spite of normal left ventricular systolic function in RA

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(10,11,12,13,14). There is little data about the use of radionuclide ventriculography in assessing left ventricular function in RA (12).

The aim of this study was to investigate cardiac left ventricular diastolic function using echocardiography and radionuclide ventriculography in a series of consecutive RA patients without clinically evident cardiovascular disease.

MATERIALS AND METHODS

Patients. Twenty-one patients (mean age: 49.9 ± 13 yrs, range 33-73; 18 female 3 male) with RA were included in the study. All of them satisfied the 1987 revised ARA criteria for the classification of RA (15). Exclusion criteria were: any clinical evidence of known cardiovascular disease (e.g. coronary heart disease, hypertension, valvular disease) or any use of drugs affecting the cardiovascular system. Five patients with RA were treated with Methotrexate, three with Salazopyrine, nine with Methotrexate and Salazopyrine in combination, and four with anti-inflammatory drugs only

Controls. Twenty sex- and age- matched controls were selected from healthy volunteers (mean age: 44.4 ± 7.7, range 33-73, 18 female, 2 male). None had any evidence of cardiovascular or immunological disease by history or clinical examination.

Clinical, Laboratory and Instrumental Investigations. A detailed history and clinical examination, routine laboratory investigations (including complete blood count, BUN, serum creatinine, alkaline phosphates, creatine phosphates, serum transaminases, C-reactive protein, ESR, serum protein electrophoresis, serum rheumatoid factor) and standard ECG were performed on all patients and controls. The patients with RA were assessed for duration of the disease, number of tender and swollen joints, duration of morning stiffness and presence of rheumatoid nodules.

Echocardiography: Each patient underwent echocardiographic examination with two- dimensional, M-mode and Doppler recordings using a Hewlett-Packard Sonos 1000 ultrasound imaging system with a 2.5 MHz transducer. Subjects were examined in the left lateral position. All M-mode, two-dimensional and Doppler echocardiographic measurements were averaged from at least three consecutive cardiac cycles. M-mode echocardiographic measurements, including left ventricular internal diastolic and systolic dimensions, left atrial anterior-posterior diameter, aortic root diameter and thickness of the interventricular septum and posterior wall, were taken according to the recommendations of the American Society of Echocardiography (16). Doppler echocardiography was employed to obtain left ventricular filling profile from transmitral flow with an apical four chamber view, with the sample volume placed at the mitral leaflet tips. Peak of early diastolic flow velocity (E), peak of late diastolic flow velocity (A) and their ratio (E/A), deceleration time (DES) (defined as the time interval required for the E velocity to decline from its peak to the baseline), isovolumetric relaxation time (IRT) (the time interval from aortic valve closure to the onset of transmitral flow) were calculated by adjusting the Doppler beam across the outflow tract.

Radionuclide Ventriculography: Radionuclide ventriculography was performed with the patient at rest in the supine position. Autologous red cells were labelled with 740 MBq technetium-99m using invivo technique. A multigated study was acquired with GE Starcam 3200 XR/T camera in the anterior, left anterioroblique and left lateral positions at rest. Images were acquired at 24 frames per cycle using 64x64 frame mode acquisition with center field of view zoom. A minimum of 4.8x10 counts was recorded in each view. Left ventricular and background regions of interests were semiautomatically drawn on both smoothed end-diastolic and end-systolic frames. The curve was obtained by weighted interpolation of end-diastolic and end-systolic curves after subtraction of the corresponding background curve. Time activity curves were filtered after background subtraction, using a Fourier expansion with three harmonics. The following parameters were calculated from the time activity curve: Left ventricular ejection fraction (LVEF); peak ejection rate (PER); time to peak ejection (TPE); peak filling rate (PFR); and time to peak filling (TPF). In addition, regional wall motion was assessed visually.

Statistical Analysis: Data was given as mean ± standard deviation. Comparisons of normal subjects and RA patients were made using Student's t test for parametric variables and Mann-Whitney test for non-parametric variables. Linear correlation was used to analyse the relationship between some clinical variables and diastolic function parameters in both echocardiographic parameters and radionuclide ventriculographic parameters. A p value <0.05 was considered as significant.

RESULTS

No differences were observed in age or sex between the groups. Epidemiological and clinical features of the RA patients are described in Table 1. None of the patients with RA had rheumatoid nodules. All patients with RA were seropositive. The heart rates of the groups did not differ.

Electrocardiography. There were no abnormalities in 12-lead electrocardiography in RA patients or controls.

M-mode echocardiography. None of the subjects had pericardial effusion or valvular disease. Left ventricular internal diastolic and systolic dimensions, left atrial anterior-posterior diameter, aortic root diameter and thickness of the interventricular septum and posterior wall did not differ between the two groups (p>0.05). M-mode echocardiography indexes are described in Table 2.

Echo-Doppler. Deceleration time was 213±71 msec in patients with RA and 196.4±25.2 msec in controls (p<0.05); the results were in the normal range for the age in both study groups (normal for age 40 and over = 160-240 msec). IRT was 85.0 ± 10.13 msec in patients with RA and 86.1±10.3 msec in controls (p>0.05); the results were in the normal range for the age in both study groups (normal for age 40 and over = 76±13 msec). E and E/A ratios were significantly lower in patients with RA than in controls (p<0.05) (normal for age 40 and over = 1.1-1.5). Echo-Doppler indexes are described in Table 3.

Radionuclide Ventriculography at rest. Systolic function of the left ventricle assessed by radionuclide ventriculography was similar in both groups. However, diastolic parameters of PFR and TPF were abnormal in patients with RA but not in controls (p<0.05). Radionuclide ventriculography indexes are described in Table 4.

Correlation between diastolic abnormalities evaluated by echocardiography and radionuclide ventriculography and clinical and laboratory variables. There was no statistically significant correlation between clinical and laboratory variables and diastolic dysfunction evaluated by echocardiography and radionuclide ventriculography (p>0.05).

Table 1. Epidemiological and clinical features of the RA patients

F/M	18/3
Age, years	49.9±13
Disease duration, years	12.5±5.1
ESH, hours	51.5±23.8
CRP, mg/dl	15.0±10.6
Morning stiffness, hours	1.8±2.3
Number of tender joints	8.2±5.2
Number of swollen joints	1.1±1.4

DISCUSSION

Mortality rates are higher in patients with RA than in the general population due to amyloidosis, renal diseases and infections (17,18). Several recent studies have reported excessive mortality from cardiovascular disease, particularly from congestive heart disease, in patients with RA (7-9), but there is still controversy surrounding this issue (17). As a result, there has been increasing interest in the study of left ventricular diastolic function in patients with RA in recent years. Several echocardiographic studies have linked RA and left ventricular diastolic abnormalities (10-14). Doppler echocardiography is a reliable and repeatable method of assessing left ventricular filling abnormalities (19), but anatomical variances of patients, for example, chest structure, and personal experience of the doctor may influence echocardiographic measurements. Echocardiographic findings were normal in our study. In Doppler echocardiography, we observed reduced E and reduced E/A ratios in our patients with RA without cardiac disease. However, because DES

Tablo 2. M mode echocardiography indexes (mean±SD) of the groups

	RA	Controls	Normal range	p
EDST (cm/m²)	2,86±0,16	2,75±0,26	<3,2	Ns
ESST (cm/m²)	1,73±0,15	1,71±0,16	<1,9	Ns
FS(%)	38,38±2,26	37,31±2,31	%30-40	Ns
Aortic root diameter (cm)	3,14±0,41	3,15±0,35	<3,5	Ns
Left atrium thickness (cm/m²)	1,97±0,13	1,88±0,19	1,2-2,2	Ns

Table 3. Echo-Doppler indexes (mean±SD) of left ventricular diastolic function in patients with RA and controls. * p<0.05

	RA	Controls
A, m/sec	0.69±0.15	0.62±0.1
E, m/sec	0.64±0.13	0.81±0.2*
E/A	0.96±0.28	1.32±0.34*
DES, msec	213±71	196.4±25.2*
IRT, msec	85.0±10.13	86.1±10.3

Table 4. Radionuclide ventriculography indexes (mean±SD) of left ventricular diastolic and sistolic function in patients with RA and controls. * p<0.05.

	RA	Controls
LVEF (%)	53.5±10.3	58.2±7.0
PER,edc/sec	3.0±0.7	2.9±0.5
TPE, msec	122.6±25.6	117.7±26.6
PFR,edc/sec	2.7±0.5	3.2±0.6*
TPF, msec	169.6±48.2	126.4±44.4*

and IRT were within normal limits, the reductions in E and E/A ratios were not regarded as predictive of diastolic dysfunction. Radionuclide ventriculography is also a reliable and reproducible method of assessing parameters of systolic and diastolic parameters of the left ventricle in individual patients, and this method is not effected by parameters associated with the patient or doctor (20). In our study, PFR and TPF, which are left ventricular diastolic function parameters in radionuclide ventriculography, were abnormal in patients with RA but not in controls. To our knowledge, there has been only one other study assessing left ventricular systolic function in patients with RA using radionuclide ventriculography; as in our study, systolic parameters were found to be normal (12).

The reasons for left ventricular diastolic ventricular abnormalities in patients with RA remain unexplained in the present study. Left ventricular diastolic function may be impaired in pericardial effusion, mitral valve disease, hypertension, coronary heart disease and in the elderly (12,21); however, our patients had none of these diseases and were middle-aged, indicating that the diastolic dysfunction cannot be due to these reasons. The diastolic abnormalities in our patients with RA were also unrelated to age, duration of disease or clinical and laboratory parameters. Previous studies have failed to detect an association between these parameters and diastolic abnormalities, suggesting that the myocardial dysfunction does not reflect the disease activity (10,12). The occurrence of diastolic dysfunction in other rheumatic and connective tissue diseases such as ankylosing spondylitis (22,23), systemic sclerosis (24) and SLE (25) indicates that diastolic dysfunction is not specific to a certain tissue type. No correlation has been found between antiphospolipid antibodies and left ventricular diastolic dysfunction in RA (13). Rowe (10) suggested that chronic inflammation of the joints might lead to the release of cytokines into the circulation, promoting the deposition or modification of connective tissue in the myocardium. Autopsy studies have reported diffuse or focal myocarditis, granulomatous lesions in the myocardium, secondary amyloidosis and signs of coronary vasculitis in patients with RA (26). Structural changes in the left ventricle may result in reduced left ventricular compliance, leading to early diastolic dysfunction (12,14). Myocardial echo was normal in our patients with RA. However, Carrooa et al. (14) and Rowe (10) found that interventricular septal thickness and left ventricular mass index were significantly higher in RA than in control groups. Rowe (10) suggested that the increase in myocardial echo in their patients with RA was due to myocardial fibrosis.

In conclusion, radionuclide ventriculography showed abnormalities in left ventricular diastolic function in our patients with RA without clinically evident cardiovascular disease, while echocardiography detected no abnormalities. Using radionuclide ventriculography may be more valuable in detecting left ventricular diastolic dysfunction in patients with RA than echocardiography. Diastolic abnormalities may be an early sign of subclinical myocardiopathy in patients with RA. The clinical significance of the left ventricular diastolic dysfunction in patients with RA is unclear in the present study. The long-term effect of early diastolic dysfunction on cardiovascular mortality remains to be proven in prospective studies.

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THE MATHIEU AND BARCAT BALANIC GROOVE TECHNIQUES: COMPARATIVE CLINICAL RESEARCH IN 46 CHILDREN

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SUMMARY

The cosmetic results and morbidity of Mathieu and Barcat techniques are presented and compared in 46 children aged five months to 19 years. The Mathieu technique was used in distal hypospadias cases with sufficiently deep and wide glans wings and deep urethral grooves, while the Barcat balanic groove procedure was employed in the remaining cases. The study was undertaken from January 1991 to July 1999. The two groups compared had equal numbers of patients.

All patients treated with the Mathieu procedure had negligible glandular hypospadias at some level. The neomeatus was slit-like or elliptical in the majority of cases. The problem of horizontal bucket handle deformity associated with the original Mathieu procedure was eliminated. Three patients had fistula, which were closed by surgery, and another three had mild stricture formation. Cosmetic and functional results were excellent with the Barcat balanic groove technique. There were no fistula formation, and only two had meatal strictures, which responded to dilatations. The Barcat technique allows anatomically superior glans reconstruction, resulting in a vertical and slit-like neomeatus in distal hypospadias repair with a low complication rate.

Key Words: *distal hypospadias, repair, childhood, boys*

ÖZET

Mathieu ve Barcat Hipospadias Onarım Teknikleri: 46 Hastada Karşılaştırmalı Araştırma

Bu çalışmanın amacı belirli ölçütlere göre seçilerek Barcat ve Mathieu teknikleri ile onarımları yapılan distal hypospadias olgularının kozmetik sonuçları ve karmaşaları esas alınarak karşılaştırmaktır.

Yaşları 5 ay ile 19 yıl arasında değişen 46 hastanın 23'ü Mathieu ,kalanlar da Barcat yöntemi ile 1991-1999 yılları arasında onarılmıştır. Uretral oluğu yeterli derinlikte olan ve glans kanatları geniş olanlara Mathieu, bu özelikleri taşımıyanlara ve kordi bulunanlara Barcat yöntemi uygulanmıştır. Bu ayırıma karşın Mathieu uygulananlarda hafif glandüler hipospadias görünümü oluşmuş, ancak orjinal Mathieu'da görülen kova sapı şeklindeki mea formasyonunun çoğunluğunda ortadan kalktığı görülmüştür. Üçer hastada fistül ve darlık oluşumu sözkonusu olmuştur. Barcat uygulanan hastalarda ise vertikal çizgi şeklinde mea olguların çoğunluğunda elde edilmiştir. Uretranın daha derine gömülmesi Barcat yönteminde fistülün oluşmamasını sağlayarak olguların bu şekilde ayrıma gidilerek onarım yönteminin seçilmesinin daha olumlu sonuçlar ortaya koyduğu görülmüştür.

Anahtar kelimeler: *Distal hipospadias, onarım, çocukluk çağı*

Hypospadias repair involves the release or correction of the chordee and the creation of a neourethra to advance the urethral meatus to the tip of the glans. In recent years, increasing emphasis has been given not only to functional adequacy but to the cosmetic results of the repair. Three basic operative approaches have been used to provide function and cosmesis at our institution. Briefly, the meatal advancement glanuloplasty (MAGPI) procedure is employed for distal hypospadias without chordee or meatal variant. In the presence of a mild chordee, either a flip-flap (modified Mathieu) or a urethral advancement procedure is employed. The results of our urethral advancement procedure has been previously reported (1).

In the Mathieu procedure, the neomeatus is located marginally lower than the exact apex of the glans, creating a slight inferior opening. The distal of the glans wings is usually tensely approximated, resulting in some disruption and leading to glandular hypospadias. Furthermore, the meatal-based flap repair creates a horizontal and rounded meatus or bucket-handle meatus that is cosmetically less acceptable than a normal, vertical slit-like meatus (2). For the reasons stated above, when the urethral groove was insufficiently de-

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ep we employed the Barcat procedure instead of the Mathieu technique and compared the results.

PATIENTS AND METHODS

Forty-six children (aged between 5 months and 19 years) with distal hypospadias were treated between January 1991 and July 1999. The average age at operation was 6.7 years. The meatus was in a subglandular or subcoronal location in all cases. Cases in which the wings of the glans were generously widened, the urethral groove sufficiently deep, the skin covering the urethral groove smooth and the ventral skin of the original urethra not shiny were considered suitable for the Mathieu procedure. We employed the Mathieu procedure as previously described by Badiola (3).

Cases in which the wings of the glans were not generously widened, the urethral groove insufficiently deep and the chordee present were considered suitable for the Barcat procedure. The distance from the meatus to the tip of the glans was defined, and a rectangular flap of ventral penile skin proximal to the urethral meatus was marked. The rectangular flap was slightly longer than the distance from the meatus to the tip of the glans. Normal saline plus 1/1000 dilution of adrenalin was injected with an insulin syringe to separate the proximal urethra and its surrounding skin. The same solution was also injected subcuticularly to the base of the urethral groove and the wings of the glans. The rectangular flap of ventral penile skin proximal to the urethral meatus was then easily elevated. The longitudinal incisions of the flap were moved forward to the tip of the glans. The strip of the urethral groove was also elevated to the apex and separated from the glandular epithelium. The chordee was then promptly excised. Glandular wings were retracted from the midline to each side. In order to place the neourethra more deeply into the penile structure, a 2-3-millimeter-deep, vertical incision was performed up to the posterior corner of the apex .

The proximal flap was turned distally and sutured to the distal flap to form a tube with a single-layer, subcuticular continuous anastomosis using 6/0 *Polydioxanone*. A neourethra was created with the aid of a 10 Fr catheter. The edges of the tube were anastomosed to the apex of the glans, creating a slit neomeatus in the sagital plane. The wings of the glans were approximated at the midline. The Buck's fascia was closed over the neourethra and the skin of the glans and penile shaft were also closed using interrupted sutures of 6/0 *Polydioxanone*. A percutaneous cystostomy was performed using a *cystofix* gauge 10 catheter. The penis was dressed with a sponge gauze. Following uretroplasy, meatoplasty and skin closure, the catheter used as a guide for the urethral model was removed. The dressings were also removed on the sixth postoperative day. The percutaneous catheter was closed, and the patient was encouraged to urinate. If there were no problems, the cystostomy catheter was then removed.

All patients treated with either the Mathieu or Barcat procedure were examined under general anesthesia. The caliber of urethra and neomeatus were checked with Hegar bougies gauge 3-4-5 one month postoperatively. Dilatation was performed if any strictures were present. In the case of fistula formation, repairs were performed three months postoperatively.

RESULTS

The Mathieu procedure was performed on 23 patients. Three patients had fistulas located just proximal to the corona that were closed by surgery. In one patient, two-thirds of the distal of the glandular wings over the neourethra was separated without any fistula or regression. Three patients had mild stricture formations, requiring three or four dilatations weekly. All other patients voided easily with a well-directed urine stream without spraying. All patients treated with the Mathieu procedure had a negligible glandular hypospadias. The appearance of the neomeatus was slightly elliptic but predominately circular in most patients.

The Barcat procedure was performed on 23 patients. There was no fistula formation, but two patients had meatal strictures. One of the patients with stricture formation had a duplicated neomeatus resulting from the fusion of the incision line of the double meatal-based flip-flaps. All stricture formations including the latter responded to one or two dilatations. The neomeatus was mainly split-like in sagital plane in 21 patients and rounded in two patients. All neomeati were located at the apex of the glans. All patients in this group voided easily with a well-directed stream without spraying. (Complications are summarized in Table 1)

DISCUSSION

The urethral meatus in the original penis is located just at the apex of the glans, appearing as a vertical slit

Table 1. Complication Rates for 46 Patients Treated for Distal Hypospadias Repair

Procedure	N	Mean Age	Fistula	Stricture	Complication rate
Mathieu	23	6.5	3 (13%)	3 (13%)	6 (26%)
Barcat	23	5.2	0	2 (8.6%)	2 (8.6%)
Total	46	6.0	3 (6.5%)	5 (10.8%)	7 (17.3%)

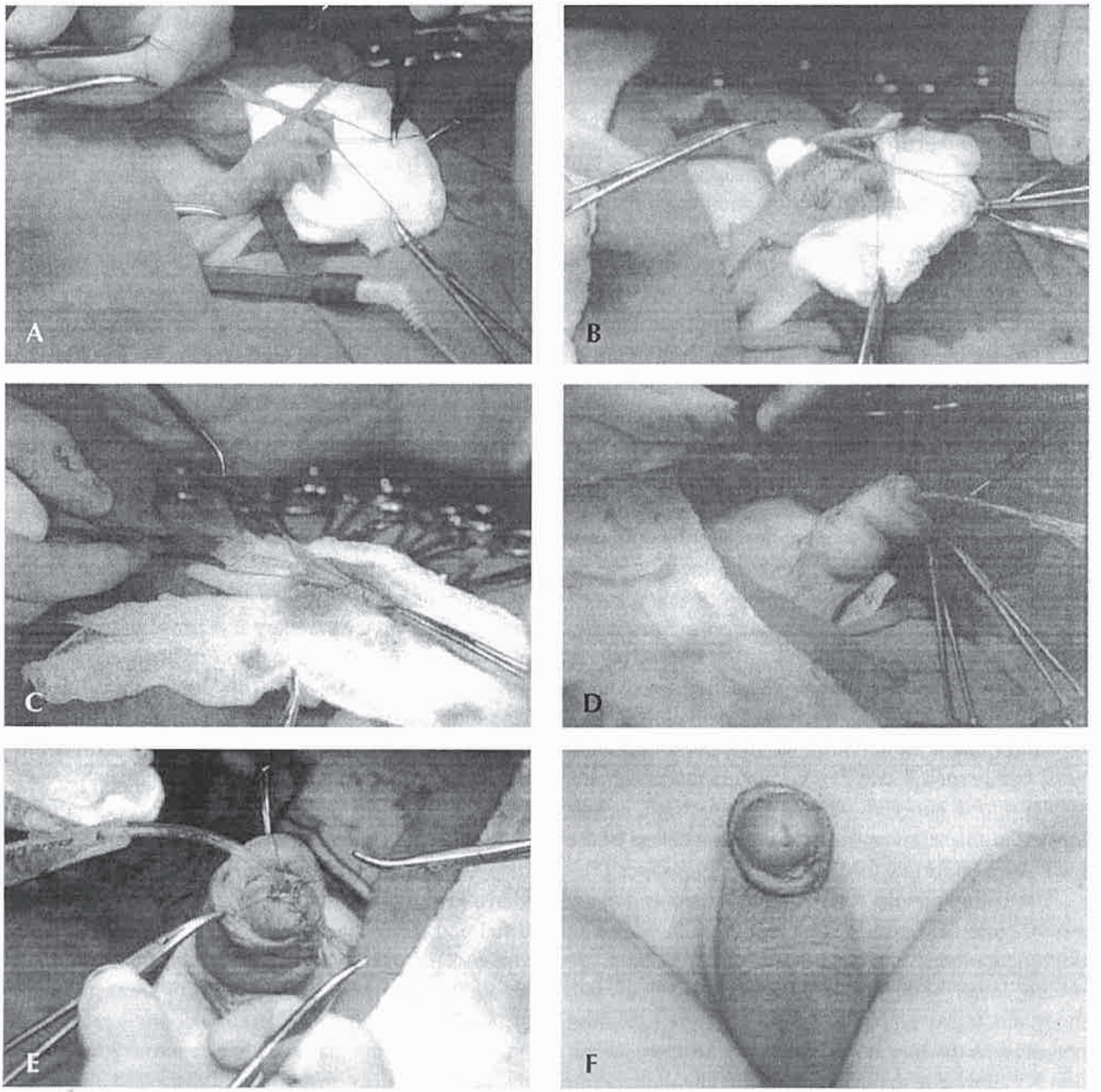

Figure 1: A: The vertical penile cutaneous and glandular epithelial flaps based at the original meatus are elevated; B: Distal flap is sutured to the neoapex following the vertical incision of glandular tissue, and two flaps are sutured on one side; C: The other side of the flaps is sutured and completed to a new urethra; D: Formation of a new meatus is completed; E: A ventral penile skin defect is closed with interrupted sutures; F: Final appearance of the neomeatus, vertical and slit-like.

in the sagital plane. However, most available methods of hypospadias surgery do not regularly form neomeati in such a manner. An elevated triangular glandular flap, anastomosed to the V-shaped incision in the mobilized urethra or to any kind of neourethra, results in a neomeatus with a wing-like shape (1). In the original Mathieu procedure, the location of the neomeatus and the final appearance of the glans are often predetermined by the shape of the glans and the depth of the urethral groove. The meatus is usually horizontal and rounded like a bucket handle (4). The meatal appearance and glandular hypospadias that we have encountered with the Mathieu procedure has not represented a phsyiological problem, but may lead to later psychological problems, the severity of which may be clarified by psychological evaluation of these patients after childhood.

Boddy and Samuel (2) described a modified "Mathieu with 'V' incision sutured" (MAVIS) procedure that resulted in the formation of a natural, slit-like neomeatus for the correction of bucket-handle deformities. In addition, Snodgrass (5) reported a method in which the urethral plate is incised from the apex of the glans to the original meatus and then tubularized. This procedure also results in a slit-like and vertical neomeatus.

This study indicated that the Barcat procedure provides the advantage of permitting the location of the neomeatus just at the apex as well as elevating a strip of urethral groove to permit correction of cordee deformity, if present. After release of the chord, part of the original urethra can be mobilized from the old meatus, as described by Koff (6), if the length of neourethra is insufficient. In addition, we propose a full-thickness, free preputial skin flap for the elongation of dorsal flip-flap. A generous vertical glans incision, as performed in this study, corrects the ventrification of the glans seen uniformly in distal hypospadias cases (7).

The complications following hypospadias surgery are stricture and fistula formation (1,3,8). Rates of urethrocutaneous fistula and stricture formation are usually lower with the Snodgrass method than with the Mathieu procedure (4). Meatal stricture formation persists with the Barcat method (9,10). Stricture formation is mainly due to features of wound healing, rather than the creation of a narrow neourethra or neomeatus. Ischemic insult to the dorsal and ventral flip-flaps and inflammation may also explain the stricture formation (2,7,8). Fortunately, stricture formation is not a serious problem. If there is no meatal regression, simple dilatation is sufficient for its treatment.

The Barcat method provides a wide, slit-like neomeatus in vertical plane, in spite of severe wound contraction. In our experience, a neomeatus of 7-10 millimeters in diameter and a generous vertical incision at the ventral aspect of the glans decrease the formation of meatal strictures. The presented method results in the formation of a slit-like neomeatus in the sagital plane, with minimal stricture formation. Circular neomeati resulted in only two cases.

The rate of fistula formation following similar techniques such as Mathieu, Snodgrass and Barcat varies between 0-21% (2,3,4,8,9,10). Detection of fistulae by physical examination can be difficult in a child who is not toilet trained. Thus, postoperative examination must be meticulous and should include distention of the urethra with the appropriate size of Hegar bougie or normal saline solution instilled through an appropriate size feeding tube one to two months after repair.

We encountered no fistula formation in double meatal-based penile flip-flap procedures in this study. However, with the Mathieu repair, some fistulae occurred at the corona. The approximation of Buck's fascia and skin over the neourethra in the Mathieu repair creates pressure that results in a disruption of the anastomosis and leads to fistula formation. By contrast, in the Barcat procedure it is possible to elongate and deepen the vertical incision on the corpus spongiosum in the midline (4,9,10). This enables the burying of the neourethra deeply at the coronal level and the approximation of the Buck's fascia and skin without tension, thus avoiding fistula formation.

Some cases in which the Mathieu technique is used in distal hypospadias repair may result in a neomeatus located slightly below the exact apex of the glans, creating a slightly glandular hypospadias. The distal part of the glans wings is usually tensely approximated and may result in some disruption, leading to glandular hypospadias. When the urethral groove is sufficiently deep, the Mathieu procedure is preferable. If the wings of the glans are not generously widened, the urethral groove insufficiently deep and a chordee present, the case should be considered suitable for the double meatal-based flip-flap procedure.

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THE CONTRIBUTION OF VITAMIN C TO HEALING OF EXPERIMENTAL FRACTURES

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Murat Arıkan* • Bülent Erdemli****

SUMMARY

The benefits of various minerals and vitamins on fracture healing have been demonstrated in animal models. Although Vitamin C is an essential substance in fracture healing, it has not been previously studied on an experimental basis. Our study randomly grouped 16 rats into vitamin C-supplemented and control groups. The right tibias of all the rats were fractured by digital manipulation. The vitamin C-supplemented group received a single high dose of vitamin C intramuscularly. On the 5th, 10th, 15th, and 20th days, two rats from each group were killed, and the tibias were examined under light microscope. It was observed that the stages of fracture healing in the vitamin C group preceded that of the control group.

Key Words: *Fracture healing, Vitamin C, Ascorbate, Experimental*

ÖZET

Deneysel Kırıkların İyileşmesinde C Vitamin'inin Katkıları

Birçok mineral ve vitaminin kırık iyileşmesi üzerindeki etkileri hayvan deneyleri ile gösterilmiştir. C Vitamininin kırık iyileşmesinde önemli rolü olduğu düşünülse de deneysel çalışmalarla ispatlanmamıştır. 16 rat kontrol ve C vitamini desteklenmiş olmak üzere rastgele iki gruba ayrılmıştır. Tüm ratların sağ tibiaları manipulasyon ile kırılmış ve sadece bir gruba bir yüksek doz intramusküler C vitamin desteği uygulanmıştır. Beşinci, onuncu, onbeşinci ve yirminci günlerde her iki gruptan birer rat öldürülerek tibiaları ışık mikroskopu altında incelenmiştir. C vitamini desteklenmiş grubun kırık iyileşmesinde bir basamak ileriden gittiği saptanmıştır.

Anahtar Kelimeler: *Askorbat, Deneysel, Kırık İyileşmesi, C Vitamini*

Fracture healing is a time-consuming event. Because fracture sufferers are disabled for prolonged periods of time, mankind has for centuries searched for ways to promote and accelerate fracture healing, with nutrition perhaps the most common area to be examined. Experiments have focused on various vitamins and minerals, the most common being vitamin D, calcium and vitamin K.

Fracture healing is preceded by chondrocyte hypertrophy and cartilage matrix calcification. A decrease in the major cartilage protein collagen type II and an increase in collagen type X due to a marked increase in alkaline phosphatase levels during the mineralization process is known to be dependent on the presence of ascorbate (1). This study attempted to determine if a single high-dosage vitamin C injection would alter the fracture-healing process in rats.

MATERIAL AND METHOD

Sixteen adult Wistar albino rats were used for the study. The animals were kept in individual cages, exposed to 12 hours of sunlight and 12 hours of darkness daily, and were all given the same brand of rat food and unlimited drinking water. The rats were randomly divided into two groups of equal numbers, an experimental group and a control group. The average weight of the rats was 249±16 grams. On the first day of the experiment the right tibias of all the rats were fractured by digital manipulation under ketamine anesthesia. Radiographs were performed to ensure uniformity of diaphyseal fractures. The experiment group received a single 0.5 mg/kg dose of vitamin C (Redoxon-Roche) intramuscularly. The animals were permitted full weight-bearing and unrestricted activity after awaking from anesthesia. On the 5th, 10th, 15th, and 20th

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days following the procedure, two rats from each group were killed and their right legs harvested. Legs were fixed with 10% neutral buffered formaline solution, and a combination of 8% formic acid and 8% hydrochloric was used to decalcify the samples. Following the conventional histologic process, 6-micrometer-thick slices were cut and dyed with hematoxylin, eosin and Mallory-Azan dyes. Histopathologic examination under Zeiss Axioscope photomicroscope was performed, and photographs were taken.

RESULTS

On examination of the fracture regions under light microscope on the 5th day, both groups revealed fracture hematoma and accompanying inflammation (Figure 1A, 1B). The vitamin C group showed chondroid cells with well-developed capillaries and granulation tissue (Figure 1B), while the control group showed more prominent inflammation with chondroid cells (Figure 1A). However, there was no major difference between the groups.

Samples taken on the 10th day from the control group showed fibrocartilaginous callus formation in addition to continuing inflammation (Figure 2A). By contrast, samples taken from the vitamin C group showed prominent hypertrophy of chondrocytes with well-developed fibrocartilaginous callus (Figure 2B).

Samples taken on the 15th day from the control group showed granulation tissue with abundant capillary formation and resorbtion of chondroid cells and fracture fragments. Fibrocartilaginous callus was present, but no osteoid tissue was observed (Figure 3A).

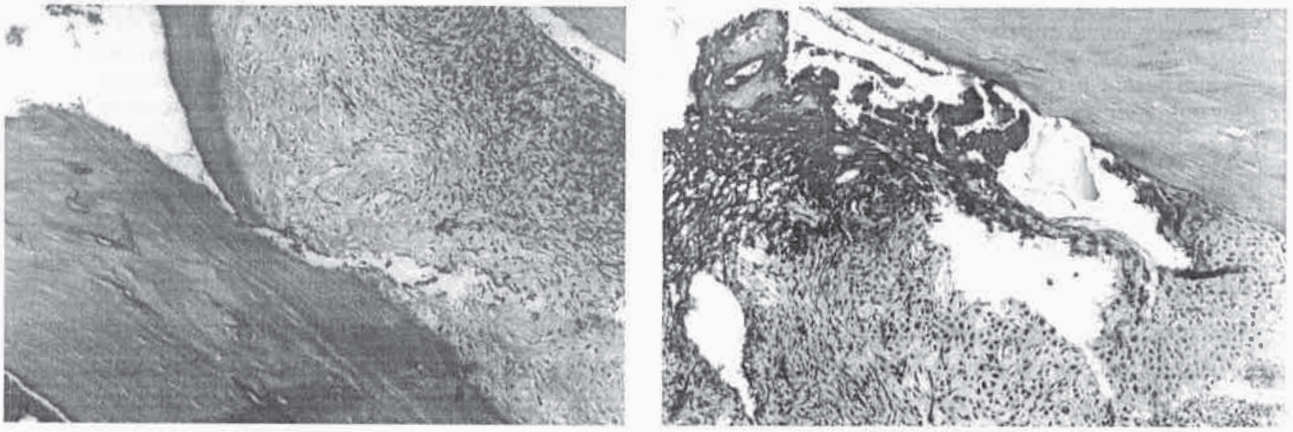

Figure 1: Examination of Specimens on the 5th Day.
A: Control group. Granulation tissue and developing chondrocytes. (HE, X25)
B: Vitamin C group. Granulation tissue, chondroid cells and abundant capillaries. (HE, X25)

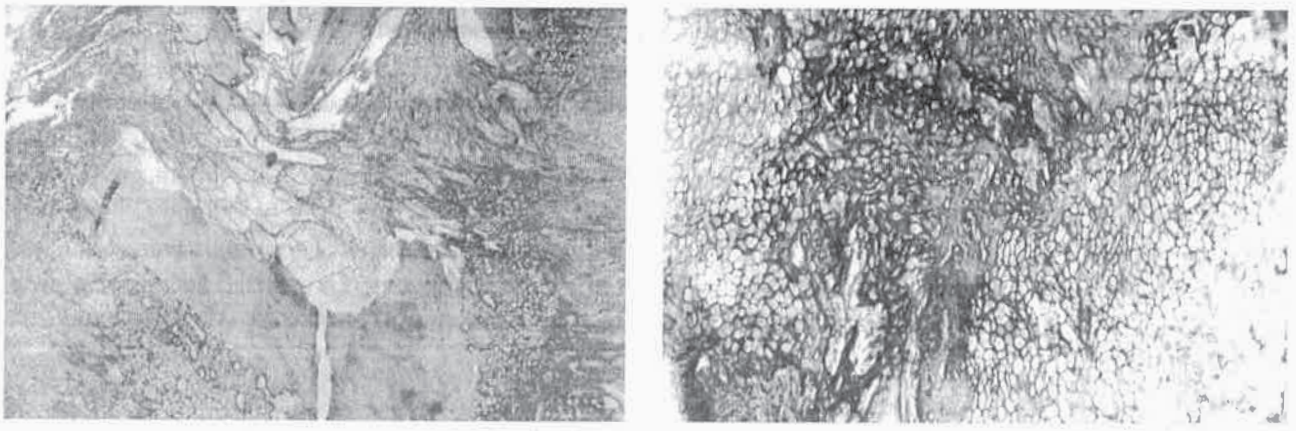

Figure 2: Examination of Specimens on the 10th Day.
A: Control group. Inflammation among fracture fragments and chondroid tissue. (Mallory-Azan, X10)
B: Vitamin C group. Hypertrophic chondrocytes and well-developed callus formation. (Mallory-Azan, X25)

The vitamin C group showed a well-developed fibrocartilaginous callus with small osteoid tissue clusters (Figure 3B).

Samples taken on the 20th day showed fibrocartilaginous callus formation in the control group and hypertrophic chondrocytes with osteoid tissue formation in the vitamin C group (Figure 4A, 4B).

DISCUSSION

Fracture healing occurs in well-defined stages. The initial inflammatory stage is characterised by the formation of a granulation tissue that provides modulation and induction of the cells that will develop capillaries. Activation of precursor cells leads to the differentiation of some cells into blood vessels, fibroblasts, chondroblasts, chondroclasts, osteoblasts and osteoclasts (2,3). The major difference between calcifying cartilage and non-calcifying cartilage is a decrease in collagen type II, the major component of cartilage matrix, and an increase in synthesis of collagen type X. As with all mineralizing tissues, alkaline phosphatase plays the major role in the synthesis of collagen type X. In a study performed by Sullivan et al, ascorbate was found to be the main inducer of alkaline phosphatase and collagen type X synthesis (1). The antioxidant characteristics of Vitamin C may also play a role in fracture healing, as indicated in an experimental study carried out by Gokturk et al, in which fracture healing was impaired by the presence of free oxygen radicals (4).

Vitamin C deficiency has also been studied. Michaelsson et al found low vitamin C intake to be a risk

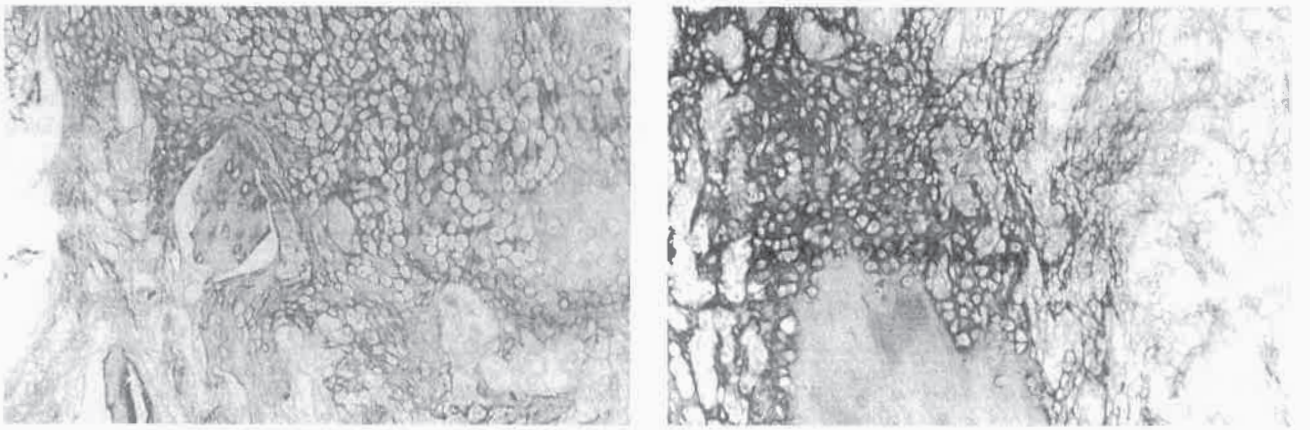

Figure 3: Examination of Specimens on the 15th Day.
A: Control group. Chondroid tissue and bone fragments being resorbed. (Mallory-Azan, X25)
B: Vitamin C group. Chondroid tissue surrounding fractured bone fragment and developing osteoid tissue islands. (Mallory-Azan, X25)

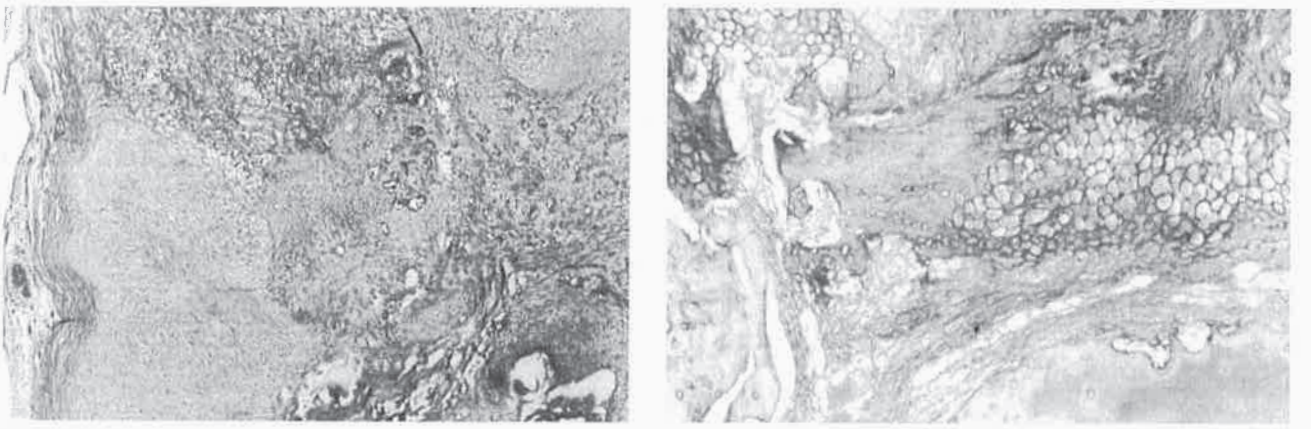

Figure 4: Examination of Specimens on the 20th Day.
A: Control group. Fibrocartilaginous callus tissue and repaired periosteum. (HE, X10)
B: Vitamin C group. Chondroid and osteoid tissue observed together in the callus tissue. (Mallory Azan, X25)

factor in hip fractures in the elderly (5). Inamo et al found highly reduced serum vitamin C levels in severely handicapped children with fractures (6). In contrast to these studies, Repasky et al found no significant correlation between vitamin C intake and fracture formation (7).

To our knowledge, the effect of vitamin C supplements on fracture healing has not been studied previously. Our study showed that, although the difference in the quality of fracture healing between the two groups was minimal, the Vitamin C-supplemented group was one stage ahead of the control group in the healing process. These findings indicate that further studies on the subject are warranted.

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A COMPARISON OF FAMILY PLANNING KNOWLEDGE AND SKILLS OF INTERNS TRAINED AT THE ANKARA UNIVERSITY SCHOOL OF MEDICINE IN 1993 AND 1996*

Ferda Özyurda • Deniz Çalışkan****

SUMMARY

Background: *This study was designed to investigate whether differences exist in the family planning knowledge and skills of interns educated at Ankara University School of Medicine in 1993 and in 1996, after the introduction of a Family Planning (FP) Counselling and Intrauterine Device (IUD) Insertion Skills Course. The study also aimed to determine the overall impact of the course on education.*

Methods: *Interviews were conducted with three groups of interns using a questionnaire designed to evaluate their FP knowledge and skills. The first group of students (308) represent 100% of interns graduated in 1993. The second and third groups of students (total 257) represent 94.1% of interns graduated in 1996 (273). The second group consists of students who had taken the FP course after its institution as an elective in 1995 (41) and the third group consists of those who did not take the course (216). The students who attended the course represent 15.9% of the total number of interns graduated in 273.*

Result: *The average number of correct answers to 20 FP-related questions rose significantly from 12.57±0.14 among interns who did not take the course in 1993 and 13.65±0.16 among interns who did not take the course in 1996 to 15.56±0.30 among those who attended the course. During the course, 82.3% of students performed gynecological examinations and 25.3% performed IUD insertions. Of all interns interviewed, 57.3% reported they had observed IUD insertions, but only 27.8% felt that they could do insertions themselves.*

Conclusion: *The rate of FP knowledge is significantly higher among those interns who attended the Family Planning Course than in other groups***. It was concluded that the Family Planning Course produced a significant increase in the knowledge and skill levels of interns, hence providing a positive impact on medical education.*

Key Words: *Family Planning, Training Skills*

ÖZET

Ankara Üniversitesi Tıp Fakültesi'nde 1993 ve 1996 Yıllarında Eğitim Gören İnternlerin Aile Planlaması Bilgi ve Beceri Düzeylerinin Karşılaştırılması

Amaç: *Ankara Üniversitesi Tıp Fakültesi'nde son sınıf öğrenciler (internler)'inin aile planlaması konusunda bilgi ve beceri düzeylerini, Aile Planlaması Danışmanlığı ve Rahim İçi Araç (RİA) Uygulama Becerisi Kursunun verilmediği 1993 yılı ve bu kursun verildiği 1996 yıllarında bilgi ve beceri düzeyinde farklılık olup olmadığını ve bu kursun etkilerini saptamak amaclanmıştır.*

Gereç-Yöntem: *Haziran 1993'te internlerin tamamına ve Şubat 1996'da %94.1'ine ulaşılarak iki ayrı zamanda, aile planlaması bilgi ve becerisini değerlendirmeye yönelik anket uygulamasına dayalı kesitsel bir çalışmadır.*

Bulgular: *İnternlerin aile planlaması ile ilgili 20 bilgi sorusundan elde edilen ortalama doğru sayısı 1993 ve 1996 yıllarında 13.01±0.11 iken kurs grubunda 15.56±0.30'dır Jinekolojik muayene yapma sıklığı %82.3 iken RİA uygulama sıklığı %25.3'tür.İnternlerin %57.3'ü RİA uygulaması izlediklerini ve yalnızca %27.8'i tek başlarına RİA uygulayabileceklerini belirtmişlerdir. Kurs grubunun ise tamamı jinekolojik muayene ve RIA uygulaması yapmışlar ve tek başlarına RIA uygulayabileceklerini belirtmişlerdir.*

Sonuç: Aile Planlaması Kursu'na* *katılanların hem bilgi hem de beceri açısından diğer iki gruba göre farklı olduğu, bir başka deyişle Aile Planlaması Kursu'nun internlerin bilgi ve beceri düzeyinde belirgin bir artış sağladığı (istatistiksel olarak) saptanmıştır.*

Anahtar Kelimeler: *Aile Planlaması,Eğitim Becerisi*

* Ankara University School of Medicine, Department of Public Health

** This study was presented at the 1st National Medical Education Congress in Ankara on 12-15 November 1998 and received recognition as the best poster at the congress.

*** The Family Planning Counselling and IUD Insertion Skills Course is abbreviated as the "Family Planning Course" or the "FP Course" throughout the rest of the text.

**** Aile Planlaması Danışmanlığı ve Rahim İçi Araç-Uygulama Becerisi Kursu, metinde kısaca Aile Planlaması Kursu veya AP kursu olarak anılmıştır.

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A study conducted in 1988 concluded that family planning education offered at schools of medicine in Turkey varies in terms of the number of theoretical and clinical sessions (1). At Ankara University School of Medicine (AUSM), the Department of Public Health and the Department of Gynecology and Obstetrics provide family planning education. Within the framework of the Project for the Strengthening of Family Planning Training jointly implemented by the Ministry of Health, Hacettepe University Department of Public Health and JHPIEGO, a Family Planning Course was instituted as an elective at the Department of Public Health of Ankara University School of Medicine as of January 1, 1995. The aim of the course was to impart practical knowledge of family planning counselling and IUD insertion skills to one group of interns per month for 10 months.

This study attempted to determine whether a difference existed between the knowledge and skills levels of interns in June 1993 prior to the course's inception and those of 1996 after the course's inception. Particular emphasis was placed on determining the extent to which taking a family planning course affected knowledge and skills.

FP information had been part of the curricula of the Department of Public Health and the Department of Gynecology-Obstetrics in the years prior to the introduction of the FP Course. It is still covered at the Gynecology-Obstetrics Department, together with clinical practice, and at the Public Health Department with the FP Course.

MATERIALS AND METHODS

This study was conducted through interviews with AUSM interns in June 1993 and February 1996. Interviews were conducted with a total of 565 students, 308 in 1993 (100% of those graduated) and 257 in 1996 (94.1% of those graduated). Of the 1996 students, 216 had taken the FP course and 41 had not taken the course. The students who attended the course represent 15.9% of the total number of interns graduated in 273.

Interns completed questionnaires they were handed by researchers. The questionnaires covered knowledge of contraceptive prevalence and legal regulations in Turkey (2 questions), oral contraceptives (7 questions), IUDs (3 questions), barrier methods (4 questions), surgical sterilization (2 questions) and subdermal implants (2 questions), for a total of 20 questions. It also included questions related to gynecological examination and IUD insertion skills, for which no marks were given. Each correct answer was awarded one point. Scores were processed using *EPI-Info Version 5* and *SPSS for Windows* software.

RESULTS

1. Demographic Characteristics of Participants

The mean age and sex distribution of the 1993 and 1996 interns were similar (1993 mean age 24.46±0.13, 1996 mean age 24.64±0.11 ($t = 0.7$ $p > 0.05$). The average age of interns (excluding 24 interns who did not specify their age) was 24.43±0.08, with 4.3% (23) in the 21-22-year bracket, 60.9% (330) in the 23-24-year bracket, 34.7% (188) in the 25-year and above bracket.

Females comprised 44.4% (251) and males comprised 55.6% (314), with no significant difference in age distribution by sex ($p > 0.05$).

Interns who had completed a Gynecology-Obstetrics internship represented 73.3% (414) of those interviewed, while 72.6% (410) had completed a Public Health internship and 20% (68 persons) had completed a Urology internship.

2. Evaluation of Participants' Family Planning Knowledge

Overall, interns answered an average of 13.20±0.10 out of 20 questions correctly. Questions on contraceptive prevalence and legal regulations had the highest proportion of correct answers at 80.6%, followed by surgical sterilization at 75.3%, oral contraceptives at 69.5%, barrier methods at 68.5% and IUDs at 50.7%. Implants constituted the least known subject at 47.7%.

Table 1 reveals that 92.7% of those in the FP Course group correctly answered the two questions related to contraceptive prevalence and legal regulations in Turkey, as compared with 82.9% of the 1996 group who did not take the course and only 77.4% of the 1993 group. The higher number of correct answers of the FP group is statistically significant ($X^2 = 13.77$ $p<0.05$).

Although no statistically significant differences were seen among groups of interns in their responses to the two questions on surgical sterilization, the FP Course group gave a higher proportion of correct answers ($X^2 = 5.46$ $p>0.05$). (Surgical sterilization was not included in the FP course syllabus until 1997).

Table 1. Percent Distribution of Responses to Questions About Family Planning Across Groups

FAMILY PLANNING QUESTION	GROUPS									STATISTICAL ANALYSIS
	FP GROUP n=41			1996 GROUP n=216			1993 GROUP n=308			
CATEGORIES	C*	W*	DN*	C	W	DN	C	W	DN	
FP and Legal Regulations in Turkey	92.7	6.0	1.3	82.9	11.1	6.0	77.4	3.8	8.8	X^2=13.77 p<0.05
Surgical Sterilization	85.4	9.8	4.8	74.3	19.0	6.7	74.7	19.5	5.8	X^2=5.46 p>0.05
Oral Contraceptives	77.7	19.5	2.8	72.8	17.6	9.6	66.1	24.4	9.5	X^2=41.91 p<0.001
Barrier Methods	71.9	25.0	3.1	71.0	17.5	11.5	66.2	19.8	14.2	X^2=21.55 p<0.01
IUDs	70.7	26.8	2.5	56.3	40.3	3.4	44.2	49.7	6.1	X^2=46.02 p<0.001
Implants	71.9	23.2	4.9	44.2	32.7	23.1	46.9	12.2	40.9	X^2=107.98 p<0.001
Total	77.2	19.8	3.0	68.3	22.0	9.7	62.9	24.2	12.7	X^2=108.00 p<0.001

*C = Correct; W = Wrong; DN = Don't Know

A study of the responses to the seven questions related to oral contraceptives reveals that the knowledge level of the group that took the FP Course is considerably higher than the other groups and that the 1996 group gave a higher percentage of correct answers than the 1993 group. The statistical significance across these three groups indicates that the FP Course has an impact on knowledge, while project activities and the integration of the FP Course into the curriculum positively affects training outside the course (X^2 = 41.91 p<0.001).

A similar correlation exists in the case of the questions related to barrier methods. The FP Course and 1996 groups gave higher proportions of correct answers (X^2 = 21.55 p<0.001).

The knowledge level on IUDs of the participants in the FP Course is significantly higher than the other groups. As with oral contraceptives, the 1996 group gave a larger proportion of correct answers than the 1993 group. Taking into consideration that the course focuses on clinical IUD insertion knowledge and skills, it can be considered successful (X^2 = 46.02 p<0.001).

The participants in the study gave a lower proportion of correct answers to questions regarding sub-dermal implants than to questions on other topics. This may be due to the fact that implants are a relatively new method and have been only recently introduced into the training program. However, the advantage of the group that took the FP Course is evident in the differences across the groups here as well. The FP Course group had a significant correct answer percentage of 71.9 (X^2 = 46.02 p<0.001).

As seen in Table 2, a comparison of points and group characteristics for all knowledge questions shows that the cohorts who took the FP Course have the highest average of correct answers compared to both the 1996 non-course group and the 1993 group (p<0.05, p<0.001). The 1996 non-course group also has a higher knowledge level than the 1993 interns (p<0.05), which is an indication that the Project for Strengthening Family Planning Training has had a positive impact on education in general.

Family Planning had been part of the curricula of the Department of Gynecology-Obstetrics and the Department of Public Health before the introduction of the FP Course. It is still covered at the Department of Gynecology-Obstetrics, together with clinical practice, and at the Public Health Department with the FP Course. Interns who have completed their rotation at either one of these departments are more knowledgeable than those who have not. In addition, the average knowledge level of interns who complete their Gynecology-Obstetrics + Public Health + Family Planning Course training is significantly higher than their peers who have not yet received training at these departments.

Gender was not a factor in interns' correct answer averages (p > 0.05).

Table 2. Distribution of Correct Answers to FP Knowledge Questions Across Groups and Comparison of Participant's Correct Answer Averages with Some Skills Criteria

		DIFFERENCE IN AVERAGES
FP COURSE STATUS		
• Took FP Course (n=41)	15.56 ± 0.30	T = 7.93*
• Did not take FP Course (n=524)	13.01 ± 0.11	p < 0.05
• Took FP Course (n=41)	15.56 ± 0.30	F = 32.25**
• 1996 (n=216)	13.65 ± 0.16	P < 0.001
• 1993 (n=308)	12.57 ± 0.14	
YEARS		
• 1996 (n=565)	13.96 ± 0.15	T = 6.52*
• 1993 (n=308)	12.57 ± 0.11	p < 0.05
COMPLETED INTERNSHIP ROTATIONS		
• Gyn-Ob only (n=104)	13.27± 0.27	F = 7.88**
• Public Health (PH) only (n=94)	12.94± 0.28	p<0.01
• Gyn-Ob + PH (n=303)	13.06± 0.13	
• Done Gyn-Ob + PH + FP (n=19)	16.05± 3.68	
• Hasn't done Gyn-Ob + PH + FP (n=42)	12.24± 0.44	
SEX		
• Male (n=251)	13.03 ± 0.15	T = 1.69*
• Female (n=314)	13.40 ± 0.15	p > 0.05
SKILLS CRITERIA		
STATUS OF GYNECOLOGICAL EXAMINATIONS		
• Done GE (n=465)	13.32 ± 0.11	T = 2.26*
• Not done GE (n=100)	12.64 ± 0.27	p < 0.05
STATUS OF OBSERVATION OF IUD INSERTIONS		
• Observed (n=241)	13.46 ± 0.13	T = 2.75*
• Not observed (n=181)	12.85 ± 0.17	p < 0.05
STATUS OF IUD INSERTIONS		
• Once (n=28)	13.00 ± 0.52	F = 5.50**
• 2-4 times (n=47)	13.51 ± 0.37	p < 0.01
• 5 times and above (n=68	14.67 ± 0.28	
CAN YOU DO SOLO INSERTIONS?		
• Yes (n=157)	13.88 ± 0.19	F = 7.66**
• No (n=376)	12.94 ± 0.13	P < 0.001
• Not sure (n=32)	12.87 ± 0.42	

*Significance test for difference in averages
**One-way variance analysis

3. Family Planning Skills Level of Participants

Of the 565 interviewees, 82.3% of the participants (465) reported having performed gynecological exams during their internship and 17.7% (100) reported never having done a gynecological examination. Of those who had experience in performing exams, 30.6% (173) reported having performed five or less, 28% (158) reported performing between 6-20 and 23.7% (133) reported performing 21 or more.

Interns who performed more than five gynecological examinations include 95.1% of the FP Course group, 55.5% of the 1996 non-course group and 62.3% of the 1993 group (Table 3). Interns who performed more than 20 gynecological examinations include 61.0% of the FP Course group, 22.0% of the 1996 group and 28.1% of the 1993 group.

As for IUD insertions by group, all interns who inserted IUDs in the FP Course group did over five insertions each. (One of the 41 participants did not practice IUD insertion and was not certified). The course program requires insertions to be done using the FP Course evaluation guidelines, and certification is contingent upon the outcome of this evaluation. Insertion of more than five IUDs by individuals rates at 32.4% in the 1996 non-course group and at 24.6% in the 1993 group.

A study of the interns' self-assurance about solo IUD insertion reveals a 100% confidence rate among those who took the FP Course. In contrast, only 19%

Table 3. Gynaecological Examination and IUD Insertion Status of Interns by Groups

	Intern Groups				
	FP Group#	1996 Group#	1993 Group#	Total#	Statistical Analysis
# OF GYN EXAMS*	n=41	n=164	n=260	n=465	
• Less than 5	4.9	44.5	37.7	37.2	X^2=33.78
• 6-20 times	34.1	33.5	34.2	34.0	p<0.001
• 21-40 times	17.1	9.8	10.0	10.5	
• More than 41 times	43.9	12.2	18.1	18.3	
# OF IUD INSERTIONS**	n=41	n=34	n=69	n=143	
• Once	0.0	26.5	27.5	19.6	X^2=61.86
• 2-4 times	0.0	41.2	47.9	32.9	p<0.001
More than 5 times	100.0	32.4	24.6	47.5	
CONFIDENCE TO DO SOLO IUD INSERTION	n=41	n=216	n=308	n=565	
• Yes	100.0	19.0	24.4	27.8	X^2=117.83
• No	0.0	75.9	68.8	66.5	p<0.001
• Not sure	0.0	5.1	6.8	5.7	

*Distribution of 465 interns who have done gynecological examinations by the number of examinations done.
**Distribution of interns who have done IUD insertions.
Colon percent

of 1996 interns who did not take the course and 24.4% of 1993 interns expressed the same confidence.

Table 4 shows the correlation of gynecological examination and IUD insertion incidence with clinical site. Interns who take the FP Course practice on the Zoe Model during the first week and real clients at the Zekai Tahir Burak Maternity Clinic during the second week. Their proficiency is evaluated by trainers who use the evaluation guidelines during practice on real clients at the Public Health Department Family Planning Service Unit. At the AUSM Department of Gynecology-Obstetrics, interns acquire practical skills during the required two-month Gynecology-Obstetrics rotation.

As can be seen from Table 4, the FP Course group, 100% of whom performed over five IUD insertions, is responsible for the main difference in the number of IUD insertions. IUD insertion figures for the groups that did not take the FP Course are similar, whether they were trained at the university Gynecology-Obstetrics clinic or at hospitals affiliated with the Ministry of Health. Regarding the number of gynecological examinations, 97.6% of the FP Course group have performed over five, as opposed to 55.8% trained at the Gynecology-Obstetrics clinic and 77% at Ministry of Health hospitals. However, as the number of gynecological examinations increases, the difference in the FP Course group becomes more evident ($p < 0.001$).

Table 4. Correlation between Gynecological Examination and IUD Insertion Status and Clinical Practice Site

	Clinical Practice Site				
	FP Course %#	Gyn-Ob Cl. %#	Other* %#	Total %#	Statistical Analysis
# OF GYNECOLOGICAL EXAMINATIONS*	n=41	n=351	n=74	n=465	
• Fewer than 5 times	2.4	44.2	23.0	37.2	X^2=46.34
• 6-20 times	34.2	32.8	39.2	34.0	p<0.001
• 21-40 times	22.0	8.5	13.5	10.5	
• More than 41 times	41.4	14.5	34.3	18.3	
# OF IUD INSERTIONS**	n=41	n=67	n=36	n=143	
• Once	0.0	25.4	30.6	19.6	X^2=61.84
• 2-4 times	0.0	47.8	41.7	32.9	p<0.001
• More than 5 times	100.0	26.9	27.8	47.5	

*Some Gynecology-obstetrics interns receive clinical training at the Gynecology-Obstetrics Clinic of Ankara Hospital or at ZTB Maternity for one month. The "other" group in the table refers to these clinical sites.
Colon percent

The correlation of interns' self-confidence for solo IUD insertion with IUD insertion practice and observation indicates that 46.3% of those who have observed IUD insertions state that they can do the procedure compared to 2.9% of those who have not observed any insertions. However, 79.7% of those who have practiced the procedure expressed self-confidence as opposed to 10.2% of those who have not.

A comparison of some skills criteria and average knowledge levels reveals a significant difference in knowledge point averages between interns who have performed and observed gynecological examinations and interns who have not and between interns who have had clinical IUD insertion practice and who believe that they can do the procedure without assistance and their peers who have had neither insertion practice nor express the same confidence in their ability to perform solo procedures (Table 2). Clearly, the knowledge level of those who have acquired the necessary practical skills is ultimately higher as well, which is supportive of the basic criteria of the training.

4. Participants' Assessment of the Coverage of Family Planning in Medical School Curricula

The final section of the study looked at the views of interns on how family planning should be offered in family planning training and medical training. The distribution of responses to the question, "How can family planning training be improved?" varies by year ($p < 0.001$). The majority of the 1993 and 1996 groups replied that more clinical practice opportunities and separate training should be provided, but the 1996 group also emphasised that the FP Course should be compulsory. Having experienced firsthand the benefits of the FP Course, the 1996 group was able to offer more concrete suggestions and found it appropriate that all students acquire the knowledge and skills the course provides. The 1993 group recommended offering more clinical training and a separate training program, a recommendation fulfilled by the implementation of the FP Course.

DISCUSSION

This study demonstrates that the FP Course integrated into the Ankara University School of Medicine's curriculum after 1995 has made a tangible contribution to the knowledge and skills of interns. The success of the course program, implemented at a large number of universities throughout Turkey in collaboration with the Ministry of Health, Hacettepe University School of Medicine Department of Public Health and JHPIEGO as a result of the "Project for the Strengthening of Preservice Family Planning Training", is evident. Findings from other programs, such as the vocational health training program offered by the Turkish Medical Association, indicate that the trainees gained knowledge but had not become proficient in clinical skills at the conclusion of the course (2). The fact that the FP Course aims to impart both theoretical knowledge and clinical skills and employs interactive training techniques combined with a humanistic approach that allows practice on models has ensured the positive impact of the training. Results of the project evaluation support the findings of this study (3).

In conclusion, it is believed that this course program, which ensures student participation, bases teaching on humanistic training principles and employs interactive training techniques, helps advance students' family planning knowledge and clinical skills. Thus, the course will ensure improved results in service delivery. It is for this reason that its countrywide expansion to reach all interns would be advantageous.

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CHORIONIC VILLUS SAMPLING (CVS): RESULTS OF INITIAL CASES

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SUMMARY

The aim of the present study was to evaluate the value and effectiveness of chorionic villus sampling (CVS) for first-trimester high-risk pregnancies. Thirty-five patients who, for various indications, underwent chorionic villus sampling were included in the cohort study. As part of the study, 12 transcervical CVSs and 23 transabdominal CVSs were performed on these high-risk patients. Two trisomy 21 (47,XX, +21) pathological karyotypes were obtained, giving a pathological rate of 5.7%. There were no spontaneous abortions in connection with the procedure. Mosaicism was not observed in any case. Although the number of patients in the study group was relatively low, it was concluded that both transcervical and transabdominal CVS are safe and reliable procedures that can be performed in high-risk women in the first trimester of pregnancy.

Key Words: *Transabdominal CVS, transcervical CVS, direct method, culture, mosaicism*

ÖZET

Koryon Villus Biyopsisi: İlk Vak'a Sonuçları

Koryon villus biyopsisinin ilk trimester prenatal tanıdaki yeri ve etkinliğinin değerlendirilmesi amacıyla , çeşitli endikasyonlar nedeniyle işlemin uygulandığı 35 hastanın sonuçları incelendi. Gebe kadınların 23 ünden transabdominal, 12 sinden ise transservikal yolla elde edilen biyopsi örnekleri, direkt ve kültür yöntemlerinin her ikisi de uygulanmak suretiyle çalışıldı. Sitogenetik inceleme sonucu, 2 olguda da trizomi 21 (47,XX,+21) saptanarak patoloji oranı % 5.7 bulundu. Hasta grubunda işleme bağlı düşüğe rastlanmadı ve mozaik bulgu gözlenmedi. Sonuç olarak; çalışma grubundaki hasta sayısının oldukça düşük olmasına karşın, transservikal veya transabdominal olarak uygulanan koryon villus biyopsisinin prenatal tanı endikasyonu koyulan gebelere ilk trimesterde 11. gebelik haftasından itibaren güvenilir olarak uygulanabileceği görüşüne varıldı.

Anahtar Kelimeler: *Transabdominal Koryon Villus Biyopsisi, Transservikal Koryon Villus Biyopsisi, Direkt Metod, Kültür, Mozaisizm*

Anxiety over the possibility of genetic disease has led to the development of new prenatal diagnostic procedures, since terminating a pregnancy is easier both medically for the physician and psychologically for the mother if it is done before the second trimester. Chorionic villus sampling is one of these new procedures.

Chorionic villus sampling is a direct method that provides the combined advantages of reduced maternal-cell contamination and rapid, direct diagnosis of some metabolic diseases by measuring the related enzymes directly from the villi samples (1).

Potential risks and reported complications of CVS include spontaneous abortion, puncture rupture of membranes, maternal sepsis, unexplained mid-trimester oligohydroamnios, preterm labor and limb-reduction defects (2,3,4).

MATERIAL AND METHODS

Thirty-five patients with fetuses ranging from 11-12 weeks (mean 11.2) of gestational age were included in the study. Maternal age ranged from 20-39 years (mean 30.5). Prenatal diagnosis indications were: advanced maternal age (n=11); congenital adrenal hyperplasia (n=4); previous child with Down syndrome (n=3); multiple malformations in a previous child (n=7); X-linked recessive genetic disease (n=7); and reciprocal translocation in the parents (n=3) (Table 1).

Transcervical CVSs were performed on 12 women and transabdominal CVSs on 23 women in the study.

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Table 1. Indications of women undergoing CVS

INDICATION	n
Advanced maternal age (>35)	11
Previous child Down syndrome	3
X-linked genetic disease in the family	7
Congenital adrenal hyperplasia	4
Translocation carriers	3
Previous child with multiple malformations	7
TOTAL	**35**

The method of obtaining the specimen was selected according to the localization of the placenta. All procedures were performed by the same operator. Between 5-30 mg (mean 20) of chorionic villus tissue were obtained from each patient (1) in at most three attempts. The procedure was performed using a 20-gauge Portex catheter introduced under abdominal ultrasonic guidance.

Specimens were taken directly to a transfer medium containing antibiotics and immediately investigated under an inverted microscope, where they were separated from maternal decidua. Both long- and short-term culture methods were used in each case. The tissue with the best morphologic appearance was placed in flasks for long-term culture and the remainder studied by direct method after incubating for 24 hours. Cultures were incubated at 37°C in an atmosphere with 5% carbon dioxide and 97% humidity. RPMI 1640, Chang's Medium and Bio AMF were used for long-term culturing media and then harvested (5). Direct-method chromosome preparation was performed according to the method of Simoni et al (1). Standart GTG was used for banding. Results of short- and long-term cultures were obtained in two and 15-20 days respectively. Fifteen metaphases were counted for each patients, and two of them were karyotyped.

RESULTS

Two abnormal karyotypes (47,XX, +21) were obtained (Table 2), giving a pathological rate of 5.7%. Both cases were induced.

A combination of both direct and culture methods were used to obtain optimal results. The direct method has the advantage of rapid results and does not carry the risk of maternal contamination risk; the culture method has a better metaphase quality and prevents incorrect cytogenetic results. Our study showed no discrepancy between long- and short-term cultures.

Table 2. Cytogenetic results of CVS

KARYOTYPE	n	OUTCOME
46,XX	10	Normal liveborn
46,XY	23	Normal liveborn
47,XX,+21	2	Induced
TOTAL	**125**	

Mosaicism confined to the placenta was not observed. In only one case, cells failed to grow because of contamination, giving a culture success rate of 97.1%. No fetal loss related to the procedure was observed, and the follow-up study revealed no preterm labor and no low birth weights in the full-term babies. No maternal complications were observed other than abdominal pain described by patients as lasting for one or two days following the procedure.

DISCUSSION

Many studies have been reported comparing chorionic villus sampling results performed on over thousands of high-risk women with other prenatal diagnosis methods such as routine genetic amniocentesis (6,7,8), especially early amniocentesis (9) that can be performed at the 14th week of gestation.

Some studies report slightly higher fetal loss rates with CVS than with amniocentesis (3,10,11), but others do not (2,4,12). Reports of fetal loss rates related to CVS ranged from 0.6-8.4% (13,14).

The problem of maternal cell contamination in prenatal diagnosis has also been noted (15). We were able to avoid this problem by using both direct method and cultures and by dissecting the villi under the inverted microscope by an experienced genetician.

Mosaicism rates have been reported at 0.83-4.3% (13,15,16), mostly due to confined placental mosaicism (CPM), with localized non-disjunction, chromosome lagging and vanishing theories put forward as explanations (16). Nevertheless, follow-up cytogenetic studies such as amniocentesis and obstetrical investigations such as ultrasound and fetal monitoring should always be considered in mosaic cases. We did not observe any mosaic cases in our patients.

Firth et al (1991) reported an increased incidence of severe limb malformations among patients undergoing CVS at 56-66 days of gestation (7,18). Other reported congenital anomalies include cleft lip and palate, encephalocele, etc. (19) Large studies were performed to evaluate these phenomena, and concluded

that they were directly related to the application time of CVS. It is now widely accepted that limb reductions can be avoided by performing the procedure after the 10^{th}-11^{th} weeks of gestation. There was no limb reduction, nor were any other maternal or neonatal complications observed in our study group.

Although our study group was small, we concluded that CVS is a safe and reliable procedure that can be performed in the fist trimester of pregnancies, reducing parental anxiety and presenting the great advantages of allowing parents to make an early decision on the termination of a pregnancy, making it easier for an obstetrician in the induction of the pathologic fetus.

CVS should optimally performed after the 11^{th} week of gestation by an experienced team, using both direct method and culturing of villi in order to avoid false positive or negative results. If results are contradictory, amniocentesis should be performed.

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EFFECTS OF SUBINGUINAL VARICOCELECTOMY ON SEMEN PARAMETERS AND KRUGER MORPHOLOGY IN SECONDARY INFERTILITY

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SUMMARY

Varicocele can impair spermatogenesis and cause infertility as a result of abnormal sperm production. Varicocele may cause a progressive decline in fertility and may occur in men who have fathered children, indicating previous fertility. This study examined the effects of subinguinal varicocelectomy on semen parameters and Kruger morphology in such men with secondary infertility. This study examined 318 couples with male factor infertility; 264 of the men had primary infertility and 54 had secondary infertility. Varicocele was present in 79 patients (29.9%) with primary infertility and 43 patients (79.6%) with secondary infertility, representing a significant difference. Microscopic dissection using a subinguinal approach was performed in patients with secondary infertility and evaluated for comparisons with results obtained in patients with primary infertility. Microsurgical varicocelectomy resulted in a significant improvement in routine semen analysis and Kruger strict morphology. Sperm parameters improved in 16 out of 20 patients (80%) with secondary infertility and 15 out of 30 patients (50%) with primary infertility, representing a significantly higher rate of improvement in patients with secondary infertile.

Key Words: *Secondary infertility, microsurgical varicocelectomy, semen parameters, Kruger morphology*

ÖZET

Subinguinal Varikoselektominin Sekonder İnfertil Hastalarda Semen Parametreleri ve Kruger Morfolojisi Üzerine Etkiler

Varikosel spermatogenezi bozabilir ve yapım bozukluğu oluşturarak infertiliteye neden olabilir. Bazı erkeklerde varikosel olmasına rağmen çocuk sahibi olabildikleri unutulmamalıdır. Bu çalışmadaki amaç prospektiv olarak subinguinal varikoselektominin sekonder infertil erkeklerdeki semen parametleri ve kruger morfolojisinin erkeklerdekî etkilerini incelemektir. Çalışmaya alınan 318 çiftin hepsinde infertilite nedeni erkeklerdi. Bunların 264 tanesinde primer infertilite ve 54' ünde sekonder infertilite mevcuttu. Primer infertilite olan hastaların 79'unda(%29.9) sekonder infertilite olan hastaların 43'ünde(%79.6) varikosel mevcuttu. İstatistiksel anlamlı fark mevcuttu. Subinguinal yaklaşımla yapılan mikroskobik diseksiyonun sekonder infertiliteli hastalarda primer infertiliteli hastalara oranla daha faydalı olduğu gözlenmiştir. Mikrocerrahi ile yapılan varikoselektomi sekonder infertiliteli hastaların 20'tanesinin 16'sında(%80) sperm parametresinde düzelme sağlamış olup bu oran primer infertilitede % 50'idi. Sekonder infertiliteli hastalardaki düzelme istatistiksel olarak anlamlı bir yüksekliğe sahipti. Varikosel fertilitede ilerleyici kötü etkilere neden olur ve mikroskobik varikoselektomi sekonder infertil hastaların sperm parametrileri ve kruger morfolojisinde belirgin düzelmeyi sağlar.

Anahtar Kelimeler: *Sekonder infertilite, Mikrocerrahi Varikoselektomi,Semen paremetresi, Kruger morfolojisi*

Varicocele may result in subfertile sperm quality characterised by oligoteratoastenozoospermia(1). The etiology of this syndrome has been described in the past as being accompanied by changes in blood supply, hormones and tissue metabolism (2,3). Moreover, varicocele is a progressive lesion whose prevalence among men with previous fertility is much higher than among men with primary infertility (4,5,6). Surgical treatment is usually recommended, and satisfactory results have been achieved in terms of improvement in both sperm quality and pregnancy rates (7). This study compared the results of microscopic dissection using a subinguinal approach in patients with secondary infertility and those with primary infertility.

PATIENTS AND METHODS

Between January 1997 and October 1998, 318 men with either primary or secondary infertility were

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evaluated for history of fertility and the presence of varicocele, diagnosed by physical examination and confirmed by Doppler ultrasonography. Those with at least one previous paternity were considered to have secondary infertility (8). None of the patients had azoospermia or urinary tract infection. The mean age of patients was 29 ± 3.9 years in the primary infertility group and 35 ± 4.8 years in the secondary infertility group. Twenty patients with secondary infertility and 30 patients with primary infertility underwent microscopic subinguinal varicocelectomy. Each patient had at least three spermiograms within the six-month preoperative period. Postoperative semen studies were obtained three and six months after varicocelectomy. Semen samples were obtained by masturbation after three days of sexual abstinence and were analysed after liquefaction. Sperm concentration and motility were determined by Makler Chamber and morphology described according to World Health Organisation (WHO) criteria and Kruger strict morphology. Semen results were averaged for each patient, and a single value was computed for each parameter. Patients were considered as candidates for surgery if they had infertility lasting longer than 12 months and any semen parameters below accepted normal levels (concentration <20 million/ml, motility <50%, normal morphological forms <40% according to WHO criteria and <6% according to Kruger strict criteria. Hormone assays were obtained in cases with severe oligospermia. Patients with bilateral atrophic testes or high levels of follicle-stimulating hormone were excluded from the study group.

Surgery was performed under local anaesthesia and intravenous sedation. A 2-cm subinguinal incision was made and the spermatic cord isolated. Dissection was performed under operating microscope or magnifier loop at 5-8X magnification. The artery was isolated and preserved using Papaverine. Meticulous dissection and ligation were performed on all spermatic veins as well as any external spermatic veins. The spermatic cord was replaced and an anatomical closure completed. Statistical analysis of results was performed using Wilcoxon rank sum tests and Chi-square tests.

RESULTS

Of the 318 men in this study, 264 were diagnosed with primary infertility and 54 with secondary infertility. Varicocele was detected in 79 patients (29.9%) with primary infertility and 43 patients (79.6%) with secondary infertility. The difference in rates between the groups was statistically significant.

Thirty patients with primary infertility underwent either unilateral (23 patients, 20 left, 3 right) or bilateral (7 patients) microsurgical subinguinal varicocelectomy. Twenty patients with secondary infertility underwent either unilateral (15 patients, 14 left, 1 right) or bilateral (5 patients) microsurgical subinguinal varicocelectomy. Varicocelectomy improved sperm parameters in 16 of 20 patients (80%) with secondary infertility and 15 of 30 patients (50%) with primary infertility. Preoperative and postoperative sperm parameters are shown in Tables 1 and 2. The change in sperm parameters following microsurgical varicoce-

Table 1. Mean Spermiogram Values in Patients with Primary Infertility

Parameter	Preoperative	Postoperative	p Value
Concentration *(x10⁶ ml)*	18.3±1.55	25.5±10.48	<0.008
Progressive motility	18.9+2.2	22.56+34.48	<0.011
Grade III motility	14.32±11	19.42±23.6	<0.028
Kruger morphology (normal forms, %)	4.11±12.3	8.33±12.5	<0.001

Table 2. Mean Spermiogram Values in Patients with Secondary Infertility

Parameter	Preoperative	Postoperative	p Value
Concentration *(x 10⁶ ml)*	15.5±3.56	23.55±31.85	<0.001
Progressive motility	14.89±32.2	21.25±48.1	<0.00
Grade III motility	11.43±21.1	20.19±16.7	<0.001
Kruger morphology (normal forms, %)	3.31±33.3	9.33±52.1	<0.00

lectomy was more significant in the group with secondary infertility.

DISCUSSION

The incidence of varicocele is higher in patients with secondary infertility than in those with primary infertility (8,9). Approximately 80% of patients with varicocele have been reported to have fathered children (10). However, prior fertility does not prevent future infertility in men. Moreover, varicocele may cause a progressive decline in fertility (11). The increase in the incidence of varicocele among men with secondary infertility may be due to either an increase in varicocele rates or a relative decrease in other etiological factors causing primary infertility (12). Our study showed higher rates of improvement in sperm parameters following microsurgical varicocelectomy in patients with secondary infertility than in patients with primary infertility. This result can be explained by the reduction of additional etiologies accompanying varicocele and a higher incidence of shunt-type (type III) varicocele in secondary infertility (12).

The effect of varicocele on fertility has been studied previously, but the focus has been on density and motility of sperm (7,8,9,12,13). Varicocelectomy has been shown to improve sperm count and appears to have variable effects on motility and morphology (14). Varicocele patients show stress patterns of abnormal sperm morphology, represented by increased numbers of tapered, immature and amorphous cells. These abnormal forms are presumably less capable of ovum fertilisation (14).

Kruger et al proposed a strict morphological classification system based upon in vitro fertilisation rates of oocytes by sperm samples partitioned by percentage of normal spermatozoa (15). To our knowledge, only two studies have reported the effect of varicocelectomy on sperm morphology as determined by Kruger criteria, and these studies examined patients with primary infertility. Seftel et al reported that sperm morphology as measured by strict morphological criteria does not improve after varicocelectomy(16), while Vazquez-Levin et al observed that correction of varicocele is associated with significant improvement in sperm morphology evaluated using Kruger criteria (17). To our knowledge, this is the first report describing sperm morphological characteristics before and after varicocelectomy evaluated by Kruger classification in men with secondary infertility. This study demonstrated a remarkable improvement in normal sperm forms according to Kruger strict morphology following varicocelectomy in patients with secondary infertility and showed that microscopic varicocelectomy, by preserving the testicular artery, is a safe and effective approach for patients with secondary infertility.

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THE PATHOPHYSIOLOGY AND TREATMENT OF KELOIDS

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SUMMARY

Keloids and hypertrophic scars represent an excessive connective response to cutaneous trauma. Genetic, immunological and biochemical factors are especially important in the pathophysiology of these fibroblastic lesions. There is no universally accepted treatment modality resulting in permanent hypertrophic scar or keloid ablation. This review discusses the etiology and clinical features of keloids and hypertrophic scars as well as the vast majority of treatment options and evolving treatment modalities.

Key Words: *collagen, hypertrophic scar, keloid*

ÖZET

Keloidlerin Patofizyolojisi ve Tedavisi

Keloidler ve hipertrofik skarlar kutanöz travmaya karşı gelişen artmış bir bağ dokusu reaksiyonudur. Bu lezyonların patofizyololojisinde genetik, immünolojik ve biokimyasal faktörler rol oynamaktadır. Hipertrofik skarların ve keloidlerin kesin bir şekilde ortadan kalkmasına yardımcı bir tedavi şekli yoktur. Bu derlemede lezyonların etiolojisi, klinik özellikleri ile ortaya çıkan yeni tedavi şekillerini de içeren birçok tedavi şeçeneği tartışılmaktadır.

Anahtar Kelimeler: *hipertrofik skar, keloid, kollajen*

Skin trauma does not always eventuate in a normal, smooth skin surface. Rather, the skin often responds to injury with a proliferation of fibrous tissue. When the tissue response is overabundant, the result is a hypertrophic scar or keloid (1). A keloid is an overgrowth of dense, fibrous tissue, usually developing after healing of a skin injury. This tissue extends beyond the borders of the original wound, does not regress spontaneously and tends to recur after excision (2).

Abnormal scarring was first described in the Smith papyrus between 2500 and 3000 BC (3). In 1817, Alibert proposed the word "*cheloide*" ("keloid") to differentiate these lesions from malignant neoplasms (4). The word is derived from the Greek word "*chele*", meaning "crab claw", referring to the manner in which these lesions grow laterally into normal tissue. Hypertrophic scars and keloids affect approximately 4.5%-16% of the black and Hispanic population (5). They have been found at a rate of up to 16% in random sampling of black Africans. In Hawaii, keloids are five times more common in Chinese than in whites. Chinese and Polynesians form keloids more frequently than Indians or Malaysians. Caucasians and albinos are less susceptible to keloids, with a white-to-black susceptibility ratio estimated at 1:3.5-1:15 (6). Keloids may appear at any age, but tend to develop between 10-30 years of age. The incidence and median age of onset are equal for both sexes (7). An estimated 300,000 patients per year are treated in the United States.

Keloid formation is principally limited to the dermis, except for the rare corneal keloid. Keloids usually appear within a year after local injury, but may also develop spontaneously, especially on the anterior aspect of the chest. The lesions are erythematous, tender, elevated, hyperpigmented, firm-to-rock hard in consistency and variably pruritic, due to their mast cell content. They appear most commonly on the upper back, chest, shoulders and earlobes. Those on the ears tend to be pedunculated, while those on the upper trunk are generally broad and raised and may have irregular, claw-like projections. Other high-incidence areas include the proximal upper limbs, the pectoral areas and the lower face (8). There are a group of disorders that should be kept in mind in differential diagnosis. These include hypertrophic scar, dermatofibroma, dermatofibrosarcoma protuberans, leiomyosarcoma, kaposi sarcoma and other sarcomas, lupus vulgaris and blastomycosis (9).

The exact genetic basis behind keloids is unknown, but some studies have shown an association with dif-

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ferent HLA types such as HLA B14, B21, BW16, BW35, DR5 and DQW3. Individuals with Type-A blood have an increased tendency to develop keloids. Transmission has been reported as autosomal dominant and autosomal recessive (10).

The most recent genetic investigations have emphasised *p53* gene mutation, which may lead to a hyperproliferative state that can result in keloid formation (11). Others have examined CD 44 receptor expression on the fibroblast cell surface functioning in fibroblast population control or the overexpression of receptors of certain growth factors (GF) such as Insulin-like GF-I and platelet-derived GF (12,13).

The role of the immune system has only recently been considered in keloid production. Among the various cytokines, a few need to be mentioned. One is interferon (IF) gamma, which downregulates collagen synthesis, and which may be deficient in individuals with a tendency to develop abnormal scars (14). A second is transforming growth factor (TGF) beta 1 and beta 2, which stimulate the production of collagen. These may be produced in excess, or there may be an abnormal sensitivity of the fibroblasts to this growth factor (15). Connective tissue growth factor is a novel peptide that acts like platelet-derived growth factor and is produced by fibroblasts after activation by TGF-beta (16).

Keloids have been reported to show some important biochemical abnormalities in comparison to normal skin (2). They are characterized by increased amounts of water, calcium, histamine, acid phosphatase, alanine transaminase, lactic dehydrogenase, alpha globulins (alpha 1 antitrypsin, alpha 2 macroglobulin), fibronectin and fibronectin messenger RNA (mRNA), elastin, glycosaminoglycans, proteoglycans (chondroitin-4- sulphate), soluble collagen, collagen deposition (type VI), proline hydroxylase, TGF-beta 1 and abnormal collagen cross-linkages. Due to increased degradation, keloids contain decreased quantities of procollagen peptides. In comparison to normal skin, keloids may contain increased, decreased or similar quantities of collagenase and collagen type III; increased or similar quantities of collagen type I and increased or similar ratios of collagen type I to III and collagen I to type I procollagen-specific mRNA; and similar quantities of type I, II, III, IV, V procollagen-specific mRNA.

Proposed scar management and prevention include three distinct therapeutic approaches: correction of abnormal collagen metabolism in those cases where the equilibrium between collagen synthesis and degradation has been destroyed; alteration of the immune/inflammatory response; and manipulation of the mechanical properties of wound repair (17).

Intralesional corticosteroid injection has been a cornerstone of both treatment and prophylaxis of hypertrophic scars and keloids (18). We commonly use triamcinolone acetonide (10-40 mg/ml). When administered independently, the response rate is between 50-100%, with a recurrence rate of 9-50% in five years. Dexamethasone-21-phosphate (1 mg/ml) has been used with a response rate of 76.5%. The majority of studies show that when corticosteroids are combined with surgery, the recurrence rate falls below 50% (19). The effect of corticosteroids may be explained in part by an interruption of the inflammatory response (20). The specific mechanism of action of corticosteroids is related to both the suppression of collagen synthesis and the release of collagenase inhibition, resulting in collagen catabolism. There are multiple side effects including atrophy, white, beadlike skin deposits and changes in pigmentation in up to 63% of patients (21).

Radiation therapy may be used alone or in combination with surgery. When combined with surgical excision in the immediate postoperative period (24-48 hours), the response rate has been reported to be as high as 97%. Radiation therapy has been associated with side effects that include local hypopigmentation or hyperpigmentation, erythema, telangiectasia and atrophy. It has been suggested that radiation is impractical for treatment of children or for areas of potential carcinogenesis such as the breast and the thyroid gland (20,22).

Effective pressure bandaging applied tightly will cause softening of the scars. Local tissue hypoxia has been proposed as the mode of action (23). Various types of pressure therapy include pressure-gradient garments made of lightweight, porous, Dacron spandex bobbinet fabric worn for 12-24 hours a day for 12-24 months; Tubigrip shaped support bandaging; and zinc oxide adhesive plaster. Overall, 60% of patients showed 75-100% improvement with these treatments. Button compression of the earlobe after excision of a keloid has been used with no recurrence at eight months to four years. Silicone in the form of cream or gel sheeting has recently been used in the treat-

ment of keloids and hypertrophic scars. Topical application of silicone gel to scars for at least 12 hours daily for approximately two to four months has been shown to be effective (24,25). Katz demonstrated that 79% of scars treated immediately after reepithelialization with silicone sheeting showed no recurrence within six months (25). The mechanism of action is still unclear; however, hydration and occlusion rather than the silicone itself are believed to play an important role (26,27,28). Chen et al found elevated levels of metalloproteinases in wound fluid collected under occlusive dressings (29). In normal wound healing, proteinases are important in degrading the extracellular matrix and thus in controlling scar formation (30). It is possible that silicone gel sheeting treatment reduces keloid formation by regulating the cytokine network (31). It has yet to be determined whether silicone-based or nonsilicone-based sheeting is more effective in the treatment of scars.

Excisional surgery alone has resulted in recurrence rates of 45-100% (19). Surgery may be combined with intralesional corticosteroid injection, radiation therapy, pressure therapy and other treatment modalities for lower recurrence rates.

Recombinant human IF gamma has been shown to downregulate collagen synthesis and may be useful in the treatment of diseases characterized by collagen overproduction (14). The most dramatic result reported was achieved when IF gamma was used after keloid excision, suggesting that IF gamma may be a useful adjunct to surgical excision of keloids to prevent recurrences (32). IF gamma side effects, including headache, reversible granulocytopenia and elevation of hepatic transaminase levels, are dose- and route-dependent (20). The mechanism of action in downregulating collagen may be related to a reduction in cellular mRNA (33, 34). Intralesional IF alpha-2b has also decreased both collagen production and glycosaminoglycans in keloidal fibroblasts, both in vivo and vitro.

Colchicine has been shown to affect collagen metabolism at three points: inhibition of collagen synthesis through disruption of microtubular systems; stimulation of collagenase; and involvement in wound contraction through a direct effect on myofibroblasts (35, 36). D-penicillamine prevents collagen cross-linking after its secretion from the fibroblast, thus increasing its vulnerability to degradation. Pentoxifylline acts by inhibiting fibroblast proliferation, but has no effect on collagenase activity (37). Antihistamines have been shown to be effective in the treatment of scars with the observation that mast cells may play a role in scar formation (38). Calcium antagonists (verapamil, trifluoperazine) may be useful in altering fibroblast shape and inducing procollagenase synthesis in keloid and normal dermal fibroblasts (39). Retinoids decrease fibroblast proliferation and collagen synthesis. Topical retinoid creams have been shown to be partially effective (40,41). Collagenase is a purified enzyme that digests collagen, the material that forms the keloid, and is widely used in the treatment of dermal ulcers, pressure sores and second- and third-degree burns. Some transient pain has been associated with injection, but there have been no apparent adverse reactions. Lipoteca, a liposomal extract of the *Centella Asiatica* plant, has been shown to have an 80% success rate in the treatment of keloids. *Centella Asiatica* is native to Madagascar and to India, where it is known as *Gotu Kola* and has a long history of use in scar treatment. Topical putrescine may be useful in modifying type III collagen cross-linking (42). The experimental drug pirfenidone has been shown to be an inhibitor of keloid proliferation in athymic nude mice (43). Topical hexadecylphosphocholine (HePC) is a phospholipid analogue that exerts a strong antiproliferative effect on neoplastic cells. It inhibits the proliferation of keloid fibroblasts in vitro and modulates their fibronectin and integrin synthesis and may therefore represent a possible therapeutic approach for keloidal scars in vivo (44). A recent study showed the presence of elevated levels of testosterone receptors in keloid tissue, suggesting that topical antiandrogen therapy might be effective (45). Tamoxifen, a synthetic, nonsteroidal antiestrogen, has been shown to inhibit keloid fibroblast proliferation and decrease collagen production through a downregulation of TGF-beta (46). The use of 5-fluorouracil intralesionally for the treatment of hypertrophic scars and keloids appears to be effective and safe, but further studies are warranted (47).

Electromagnetic fields (EMFs) inhibit type I and type III collagen synthesis and decrease the expression of TGF-beta in keloidal fibroblasts, suggesting that EMFs may have useful therapeutic potential in the treatment of keloids (48). The therapeutic effects of cryotherapy are related to direct cell damage as well as to changes in the microcirculation initiated by freezing, which leads to stasis of blood and subsequent dermal

anoxia, resulting in tissue necrosis and sloughing. Keloids that have greater blood flow by Doppler and those that are more erythematous and of more recent onset responded better to treatment. Zouboulis et al, in their randomized prospective study of 93 white patients with keloids and hypertrophic scars, found no recurrences in an average follow-up period of 32 months (49). Side effects were limited to hypopigmentation and light-to-moderate atrophy. The hypopigmentation is due to cold sensitivity of melanocytes and is permanent, making cryotherapy a less desirable option for dark-skinned patients.

The development of laser technology represents perhaps the most promising treatment modality for the cosmetic and functional improvement of scars. The argon laser was one of the first lasers used in the treatment of keloids. It was thought to work by coagulation of the capillary plexus, leading to an area of local anoxia. The decrease in pH that occurs with the production of lactic acid by glycolysis results in the release of collagenases, leading to increased collagenolysis (50). Hulsbergen-Henning et al postulated that the results were only temporary, due to the superficiality of the treatment (51). Bailin first reported good results with keloids excised using continuous-wave CO_2 laser in 1982 (52). In 1991 Norris further evaluated the efficacy of CO_2 laser excision, concluding that it is not successful in suppressing the growth and recurrence of keloids (53). Olbricht and Arndt concluded that CO_2 laser excision should be reserved for special conditions such as large or draining keloids that need to be debulked before other measures can be taken to control regrowth (54). The neodymium: yttrium-aluminum-garnet (Nd:YAG) laser has been shown to exert an effect on collagen metabolism. Collagen production was shown to be selectively inhibited through a direct photobiological effect, while DNA replication and cell viability of fibroblasts were unchanged (55).

Over the past 10 years, great strides have been made with the use of the 585-nm vascular-specific flashlamp-pumped pulsed dye laser in the treatment of hypertrophic scars and keloids. The first study demonstrating successful scar treatment came from Alster et al in 1993 (56). Improvement in the scars persisted, with no recurrence in the four years following treatment (57). There is no consensus on the mechanism of scar improvement produced by this laser. Some theories suggest decreased cellular nutrition and function within the scar, leading to a decline in microcircular perfusion and alteration of the collagen metabolism, resulting in catabolism (58). The effectiveness of the 585-nm laser may also be related to the regional increase of mast cells observed after laser irradiation (59). Individuals with skin phototypes I or II are the best candidates, as dark-skinned patients have increased amounts of melanin, which competes with hemoglobin for absorption of laser energy. The most appropriate timing of treatment has yet to be determined, but treatment of scars within the first month after surgery or trauma may prevent hypertrophy in keloid-prone patients (57,60,61,62).

The variety of methods used in the treatment of keloids and hypertrophic scars indicate that a combination of surgical and nonsurgical treatment modalities may provide the best results both for treatment and prevention of recurrences.

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PERSISTENT HYPERINSULINEMIC HYPOGLYCEMIA OF NEONATES*

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SUMMARY

Hyperinsulinism, although rare, is the most common cause of persistent hyperinsulinemic hypoglycemia in infancy. Because of persistent hypoglycemia, serious difficulties are encountered in the management and follow-up of this clinical condition.

A male neonate, after an uncomplicated full-term pregnancy, was admitted to another hospital with convulsions on the 3rd post-natal day. He had been diagnosed and treated for meningitis, was treated with phenobarbital, and was discharged from the hospital. At 3-months old he was referred to our department for persistent convulsions and lethargy. His parents were of 1st degree of consanguinity. His blood glucose level was found to be 24 mg/dl. Because of the dangerously high insulin level during hypoglycemia (insulin/glucose > 0.3), the absence of ketonuria, and the need for a high dose of glucose infusion (> 15 mg/kg/min) to achieve normoglycemia and a glycemic response to glucagon despite the hypoglycemia, a diagnosis of persistent hyperinsulinemic hypoglycemia of infancy was made. Prednisolone, glucagon, diazoxide, and long-acting somatostatin analog-octreotide were ineffective in restoring normoglycemia. It was decided to perform a subtotal pancreatectomy (80%). The histopathological examination of the pancreas revealed diffuse adenomatous hyperplasia (nesidoblastosis). Intermittent hypoglycemic episodes continued following the operation. Normoglycemia was achieved and maintained with a low dose of octreotide. He is now in the 6th post-operative month and developmentally normal.

Key Words: *Hyperinsulinemic hypoglycemia, nesidoblastosis*

ÖZET

İnfant Dönemi Hiperinsülinemik Hipoglisemi

Hiperinsülinizm, ender olmasına karşın, infant dönemi kalıcı hiperinsülinemik hipogliseminin en sık nedenidir. Kalıcı hipoglisemi nedeni ile, bu klinik antitenin takip ve tedavisi önemli zorluklar içermektedir.

Komplikasyonsuz miad gebeliği takiben doğan bir erkek bebek doğum sonrası 3. günde konvülsiyon nedeni ile başka bir hastaneye kabul edilmiş. Olgu, menenjit tanısı alarak tedavi edilmiş, fenabarbital başlanmış ve hastaneden taburcu edilmiş. Olgu devam eden konvulsiyon ve letarji nedeniyle departmanımıza sevk edildiğinde 3 aylık idi. Olgunun anne ve babası 1. dereceden akrabaydı. Kan şekeri 24 mg/dl idi. Hipoglisemi sırasında uygunsuz yüksek insülin düzeyi (insülin / glikoz > 0.3), ketonüri olmaması, normoglisemi sağlamak için yüksek doz glikoz infüzyonu (> 15 mg/kg/dak) ve hipoglisemiye karşın glukagona glisemik yanıt olması nedenleri ile, infant dönemi kalıcı hiperinsülinemik hipoglisemi tanısı konuldu. Prednizolon, glukagon, diazoksid ve uzun-etkili somatostatin analoğu octreotide normoglisemiyi düzeltmede etkisiz kaldı ve subtotal pankreatektomi (%80) uygulanmasına karar verildi. Pankreasın histopatalojik incelemesinde diffüz adenomatoz hiperplazi (nesidioblastosis) saptandı. Operasyon sonrası aralıklı hipoglisemik episodlar devam etti. Düşük doz octreotide ile normoglisemi saptandı ve sürdürüldü. Olgu şimdi post-operatif 6. ayda ve gelişimsel olarak normaldir.

Anahtar Sözcükler: Hiperinsülinemik hipoglisemi, nesidioblastoz

Hypoglycemia is the most common metabolic problem in childhood and, when severe or recurrent, devastating neurological sequelae may occur (1). Severe consequences of hypoglycemia are seen when the cause is hyperinsulinism. Not only the brain is deprived of glucose, but the excessive insulin secretion also switches off lipolysis and ketogenesis, resulting in a deprivation of a supply of alternative fuels for the brain (2). Hyperinsulinism accounts for approximately 1% of all cases with hypoglycemia (3), but it is the

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most common cause of persistent hyperinsulinemic hypoglycemia of infancy (PHHI). PHHI is also called by other names such as islet cell dysmaturation or dysplasia syndrome, congenital hyperinsulinism, and, previously nesidioblastosis (4). The incidence is reported to be 1 in 50.000 live births (5). The pathogenesis of PHHI remains unknown (6-9). Although most cases are sporadic, it is now well recognized that the disorder may be familial (10). Advances in the molecular genetics of PHHI have revealed abnormalities of sulphanylurea receptor (SUR) gene located on the short arm of chromosome 11; this may explain insulin hypersecretion in such familial cases (11,12). The absence of functional K^+_{ATP} channels has recently been shown to induce insulin hypersecretion in sporadic PHHI (13).

The aim of therapy is to maintain euglycemia to protect the developing brain from possible damage (14). Diazoxide, somatostatin or a long-acting analog and glucagon, each alone or in various combinations, have been used with varying degrees of success (4, 15-21). Many children require surgery early in life in the form of a sub-total or total pancreatectomy if medical treatment fails to maintain euglycemia (9,15). The results of surgery vary according to the extent of the pancreatic resection (15).

In the present article, we report the case of a 3-months old infant with PHHI who underwent a sub-total pancreatectomy after failing to respond to currently available medical treatments.

CASE REPORT

A male neonate, delivered full term with a birth weight of 4000 grams and following an uncomplicated pregnancy, was admitted with convulsions to another hospital in the 3rd post-natal day. Meningitis was suspected at that time and treatment, including phenobarbital for his convulsions, was begun. He was referred to our department at age 3 months because of ongoing seizures and lethargy. He was hospitalized to determine the causes of his condition and his blood glucose level was found to be 24 mg/dl.

The patient is the 3rd child of 1st degree consanguineous parents. His height was in the 50-75th percentile, his weight was in the 75-90th percentile and his head circumference was in the 10th percentile. Except for mild hepatomegaly, the physical examination was normal. Biochemical data is shown in Tables 1 and 2. Observing the inappropriate insulin increase during hypoglycemia, the absence of ketonuria, and an exaggerated response to glucagon test eliminated the causes of hypoglycemia, and, thus, the diagnosis of hyperinsulinism was confirmed. A pancreatic sonography (US) and the magnetic resonance imaging (MRI) were normal. Glucose infusion at the rate of > 15 mg/kg/min to restore normoglycemia was initiated.

The hypoglycemia persisted and prednisolone at 2 mg/kg/day was also given. Normoglycemia could not be achieved, despite this treatment. Because of an observation of Cushingoid findings, the prednisolone, by titration, was withdrawn from the treatment. It was decided to administer diazoxide at 12 mg/kg/day. No response to the treatment with diazoxide was observed, and the dose was increased to 20 mg/kg/day. It was also ineffective in maintaining normoglycemia. In addition, hypertrichosis occurred. The patient was placed on a subcutaneous infusion of octreotide at 10 mg/kg/day via a portable pump. The dose was titrated up to 20 mg/kg/day. This again failed to achieve the desired results. A combination of octreotide at 20

Table 1. Laboratory characteristics of the patient

	The case	Normal values
Glucose (mg/dl) (*)	32-29	> 50
Insulin (mU/ml) (*)	16-29	< 10
Insulin/Glucose (*)	0.5-1	< 0.3
Blood pH	7.4	7.35-7.45
Lactate (mmol/L) (*)	2.0	0.7-2.1
Ammonia (mmol/L)	36	21-50
Growth hormone (ng/ml) (*)	17	> 10
Cortisol (mg/dl) (*)	18	5-24
ACTH (pg/ml)	45	10-100
Triglycerides (mg/dl)	81	30-86
Total cholesterol (mg/dl)	155	45-182
Urinary amino acids	Negative	Negative
Urinary ketone (*)	Negative	Negative

(*) Samples obtained during the acute hypoglycemic episode

Table 2. Results of the glucagon test

Minute	Glucose (mg/dl)
0	41
30	113
60	133

mg/kg/day and glucagon at 100 mg/kg/day was also ineffective in stabilizing his blood glucose. Surgical treatment was decided upon and an 80% pancreatic resection was performed. The histopathological diagnosis of diffuse adenomatous hyperplasia (nesidioblastosis) was made (Figures 1, 2).

Hypoglycemic values persisted post-operatively. A subcutaneous injection of octreotide at 5 mg/kg/day, four times daily, achieved a correction of his hypoglycemia.

The octreotide dose was titrated down to 2 mg/kg/day at follow-up. It is now his 6th post-operative month and he is developing normally.

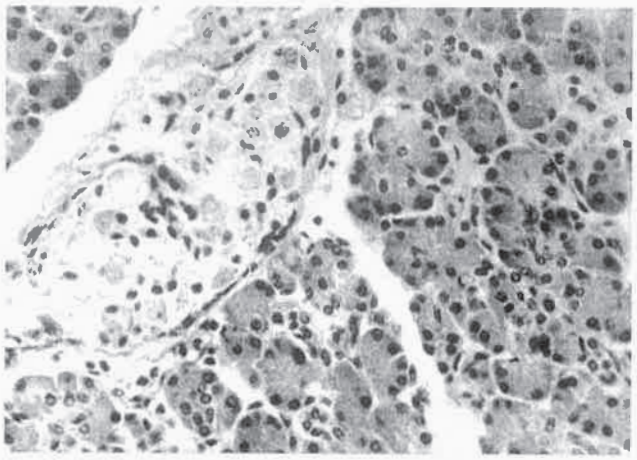

Figure 1: Obvious nuclear hyperplasia and polymorphism in endocrine pancreatic islets; PAS X 400.

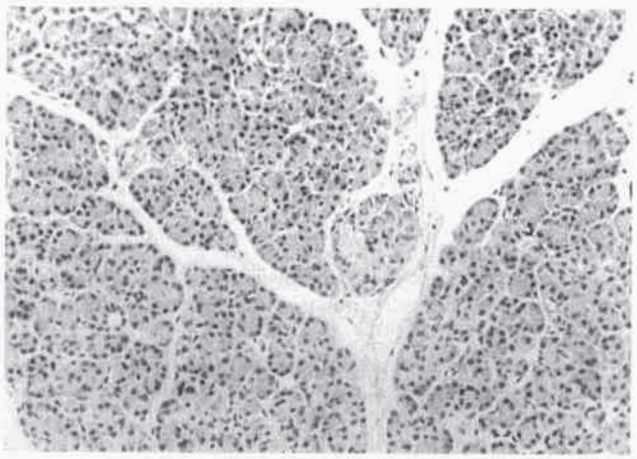

Figure 2: Endocrine pancreatic islets with obvious nuclear hyperplasia in pancreas separated with connective tissue bands; HE X 200.

DISCUSSION

PHHI is one of the most difficult metabolic problems in pediatrics. The criteria to diagnose hyperinsulinism include the presence of low plasma free fatty acids and ketone bodies, simultaneous inappropriate plasma insulin release during hypoglycemia, a glycemic response to glucagon, despite hypoglycemia, and the need for a glucose infusion above 10-15 mg/kg/min to achieve normoglycemia (22). Excess insulin increases the hepatic glycogen synthesis, which is probably one of the factors responsible for hepatomegaly (23). Some infants have high birth weights due to the anabolic effects of insulin; the weights and heights of these children are generally greater than those of normal children (24). Our findings that the patient was large for his gestational age and had mild hepatomegaly in the physical examination supported a hyperinsulinemic presentation. The biochemical data of our case also confirmed the diagnosis of hyperinsulinism. In our case, as was expected in cases of hyperinsulinemic hypoglycemia, glucose infusion in high doses was needed in order to reverse this condition.

Two forms of PHHI have been reported (9, 25). One is characterized by focal pancreatic adenomatous hyperplasia (focal PHHI) and the other is characterized by a diffuse b-cell abnormality (diffuse PHHI). Whilst diffuse involvement of the pancreas is more common in infancy, localized lesions are seen with more frequency in older children (15). The US, computed tomography and MRI are helpful in diagnosing adenoma if it is echogenic (23). The pancreatic US and MRI of our patient revealed normal findings.

Diazoxide mobilizes glucagon, stimulates catecholamine secretion, and directly inhibits insulin release by inhibiting SUR (4, 15, 17). Glaser et al. reported only 3 of 18 patients in whom hypoglycemia was controlled with diazoxide alone (16). It is usually ineffective in cases with recessively inherited hyperinsulinism, because the mechanism of diazoxide action requires a normal SUR (17). Normoglycemia could not be restored in our case, although diazoxide was increased to its recommended highest dose. Because our patient was the child of 1st degree consanguineous parents and there was no response to diazoxide treatment, it is likely that our case presents an autosomal recessive pattern of inheritance of hyperinsulinism. Unfortunately, we did not have the opportunity to perform molecular genetic studies at our hospital.

Glucagon and somatostatin produce a prompt and significant increment in glycemia in cases with PHHI (4). Somatostatin suppresses insulin secretion further downstream at the level of calcium-mediated insulin release (17). A tolerance to somatostatin may develop with long-term treatment (26). A review of all the reported cases suggested that only one fourth to one third were successfully treated with octreotide (4). Long-term management with combined subcutaneous octreotide and glucagon infusion has been reported as being used to avoid surgery and to stabilize blood glucose levels in very refractory cases (21). Despite the use of octreotide with increasing doses, and later together with glucagon, normoglycemia could not be achieved in our patient. No side effects due to octreotide were observed.

Hypoglycemia in cases with PHHI may result in brain damage, especially during episodes of stress or recurrent infection (15). Thomas et al. found at least 50% of infants undergoing pancreatic resection were mentally retarded at the time of surgery (3). The time interval between the onset of symptoms and the operation was 5.55±1.53 months in developmentally normal children when compared with 9.65±2.6 months in those mentally retarded (3). For this reason, in patients in whom normoglycemia cannot be maintained, despite optimal medical treatment, surgical resection should be performed early, and not as a last resort (15). Because our patient did not respond to medical treatment, he underwent a surgical resection at the age of 6 months.

A surgical resection involves a subtotal pancreatectomy in most patients. Martin et al. reviewed the results according to the extent of pancreatic resection in 181 patients (27). Of 118 cases that underwent subtotal (<80%) resection, 45% required additional treatment and 26% needed another operation for persistent hypoglycemia. Of 63 patients having near total (>80%) pancreatectomy, in comparison, only 20% required additional medication and 8% needed another operation. Thomas et al. reported that, of 159 cases, 28% of the patients who had received a subtotal pancreatectomy needed a second operation when compared with 5% of patients with a 95-98% pancreatectomy (28). Some researchers recommend an initial 95% pancreatectomy in all patients (29). A nearly total pancreatectomy may result in an unacceptably high recurrence risk if not sufficiently complete and, conversely, if too complete, the result is malabsorption and diabetes mellitus (16,30). Our patient underwent a subtotal (80%) pancreatic resection. As the pancreatic lesion was diffuse and a subtotal pancreatectomy was performed, the post-surgical success to maintain normoglycemia could not be achieved, which was not an unexpected result. Octreotide 5 mg/kg/day was begun and this corrected the patient's hypoglycemia. At follow-up, the drug dose was decreased to 2 mg/kg/day. Our patient is now normoglycemic. Whether or not he will be in need of another operation is a matter of debate at present, and will be clarified at follow-up.

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FIBROUS HAMARTOMA OF INFANCY IN THE INGUINAL REGION

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Selim Erekul • İ. Haluk Gökçora***

SUMMARY

We present a 17-month-old boy with a fibrous hamartoma of infancy in the inguinal region. The rare occurrence of the lesion in this region, the preoperative diagnostic dilemmas, and differential diagnoses will be discussed.

Key Words: *Hamarotma, fibrous hamartoma, inguinal region mass, childhood*

ÖZET

İnfantta İnguinal Bölgede Fibröz Hamartom

Çocukluk çağında çok seyrek rastlanan inguinal bölgede fibröz hamartom olan 17 aylık bir erkek çocuğu sunulmuştur. İnguinal bölgede nadir rastlanan bu patolojide yaşanabilecek preoperatif tanısal güçlükler ve ayırıcı tanıda yaşanabilecek zorluklar tartışılmıştır.

Anahtar Sözcükler: Hiperinsülinemik hipoglisemi, nesidioblastoz

Fibrous hamartoma of infancy is a rare, subcutaneous, soft tissue tumor that occurs most commonly in the shoulder region (1). It was first described by Reye as a "sub dermal fibromatous tumor in infancy" in 1956(2). It was later defined as a distinct clinicopathological entity. It typically affects boys under the age of 2 years (3). Local excision is usually curative, but occasionally, local recurrences may be seen. Here we present an inguinal fibrohamartoma, which caused preoperative diagnostic difficulties.

CASE REPORT

A seventeen-month-old boy was admitted because of a right inguinal mass. An examination revealed a soft, irregular, painless, blue-purple 10 x 4 x 2 cm. mass in the right inguinal region and lower hemiscrotum, extending to the distal part of the inguinal sulcus (Fig. 1). Upon palpation, the testis and vas deferens were separate from the tumor. The rest of the physical examination was normal. The first impression was concomitant with a hemangioma. In the ultrasound examination, a hypo echoic mass, distinct from the major vessels, was found. An ultrasound of the abdomen and pelvis revealed no evidence of disease elsewhere. The region of the tumor was explored via an inguinal sulcus incision. An infiltrative gray-yellow subcutaneous fibrolipomateous lesion was found (Fig. 2). After a total excision of the tumor, the histopathological examination revealed bands of mature fibrous tissue, lobules of adipose tissue and regions of loosely arranged spindle-shaped immature mesenchymal cells with a myxoid background (Fig. 3). The postoperative period was uneventful. The follow-up showed no recurrences of the lesion.

DISCUSSION

Fibrous hamartoma of infancy is a distinct fibroblastic proliferation. It typically occurs in the shoulder or axillary region of male infants (1,3,4). However, the genital area may also be affected, resulting in a clini-

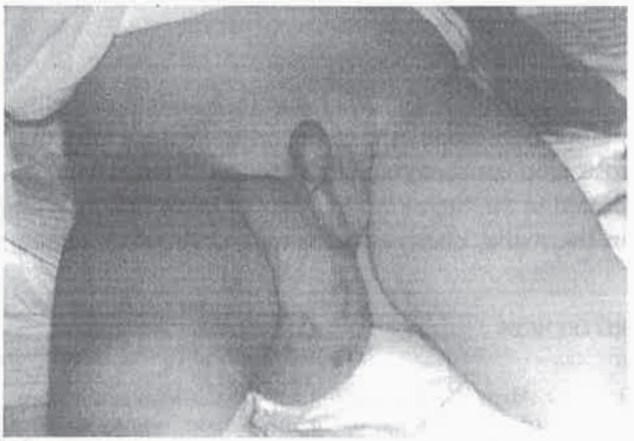

Figure 1: A 10 x 4 x 2 cm mass located in the right inguinal region

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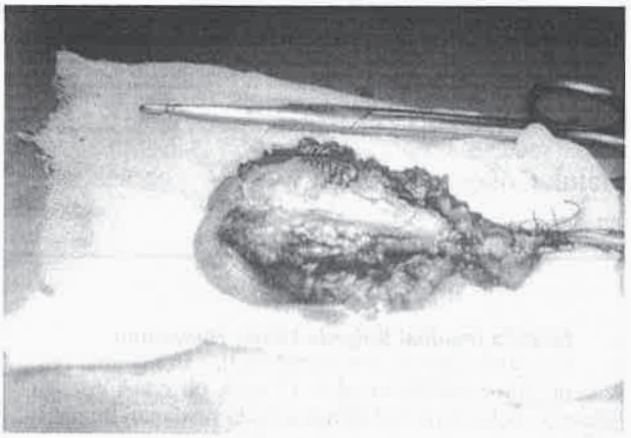

Figure 2: The cross section of the mass demonstrating a fibrolipomateous structure.

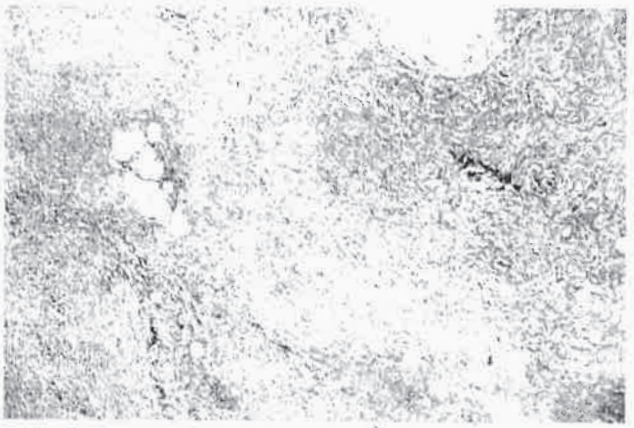

Figure 3: Histopathological view of the lesion (H&E x100) note bands of mature fibrous tissue, lobules of adipose tissue and regions of loosely arranged spindle-shaped immature mesenchymal cells with a myxoid background.

cal presentation that may mimic lymphadenopathy, rhabdomyosarcoma, hemangioma, infantile fibromatosis, and liposarcoma. Until 1999, 197 cases were reported in the literature (5). Most of these tumors were in the axilla, chest, upper arm and shoulder region. Our case was one of the few inguinal region sited fibrous hamartomas. The physical examination and ultrasound had led us to a diagnosis of a hemangioma. Both of these lesions, including fibrous hamartomas, may present as a subcutaneous, round or ellipsoid, discrete nodules that are seldom fixed to the underlying fascia or muscle. In addition, the US images of these tumors may mimic each other. The deep dermal and subcutaneous location of a fibrous hamartoma of infancy may result in a fixation of the overlying skin, but usually the mass is moves freely and does not involve the dermis.

The tumor may grossly appear as fatty, fibrous, or fibrolipomatous, depending on the proportion of the component tissue types (6). This case presented with a fibrolipomatous appearance. These tumors range from a size of between 3-5 cm. but some may exceed 15 cm, as in our case, which was 10 x 4 x 2 cm.

The histological features of these lesions are usually constant, as in this case; it had bands of mature fibrous tissue, lobules of adipose tissue, and regions of loosely arranged, spindle shaped, immature mesenchymal cells with a myxoid background.

Because of the risk of recurrence of a fibrous hamartoma of infancy, although it is rare, complete excision is indicated. During the procedure, it is sometimes difficult to differentiate a fibrous hamartoma from rhabdomyosarcoma or a melanotic neuroectodermal tumor of infancy. Doing a frozen section during surgery may help in directing the procedure.

In conclusion, a fibrous hamartoma of infancy may be observed in the inguinal region. A differential diagnosis should include myofibromatosis, fibromatosis, fibro Arkoma, neurofibroma, rhabdomyosarcoma, and a melanotic neuroectodermal tumor of infancy, hemangioma, and pseudosarcomatous myofibroblastic proliferation. Total excision of the tumor should resolve the condition. After complete excision, the recurrence rate is unlikely.

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LUPUS ERYTHEMATOSUS PROFUNDUS IN A PATIENT WITH DERMATOMYOSITIS

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SUMMARY

Lupus erythematosus profundus (LEP) is an unusual variant of cutaneous lupus erythematosus characterized by chronic, recurrent inflammation of the subcutaneous tissue. We here present a case of LEP associated with dermatomyositis.

Key Words: *Lupus erythematosus profundus, dermatomyositis*

ÖZET

Dermatomyositis'te Lupus Eritematozus Profundus

Lupus eritematozus profundus (LEP), kutanöz lupus eritematozusun ender bir formu olup, subkutan dokunun kronik ve tekrarlayan inflamasyonu ile oluşur. Burada dermatomyozit ile birliktelik gösteren bir LEP olgusu sunulmaktadır.

Anahtar Kelimeler: *Lupus eritematozus profundus, dermatomyozit*

Lupus erythematosus profundus (LEP), also called lupus panniculitis, is an unusual but distinctive clinical variant of lupus erythematosus in which the cutaneous inflammatory reaction occurs primarily in the deeper dermis and the subcutaneous fat. It may develop in patients with discoid LE or SLE or may occur as an isolated phenomenon (1-5). We here present a case of LEP associated with dermatomyositis.

CASE REPORT

A 31-year-old female was admitted to our clinic because of persistent skin lesions. The first lesion had developed over the past six months on her right hip. It had begun as a tender, slightly erythematous induration with a slowly growing depression. Over the past four months, a second, similar lesion developed at the ventral side of the thigh. The patient's present illness started without any trigger. She did not notice any systemic symptoms. She had been treated with topical steroids for these lesions, but it had not been at all effective. Past medical history was significant for dermatomyositis since 1996.

We successfully treated the patient's skin lesions with prednisone and azothioprine. She has remained in remission for the last eight months, and tests for autoantibodies relevant to dermatomyositis were negative.

Upon physical examination the patient appeared well, and there were no systemic abnormalities. Examination of the skin revealed an indurated, slightly depressed lesion on the ventral thigh measuring 5x10 cm in its largest diameters. A smaller but deeper depression located on the right hip measured approximately 5x5 cm. The skin in this area was firmly attached to the subcutaneous layers and showed clinically less inflammatory activity (Fig.1). The patient did not have any other skin lesions.

Laboratory data including complete blood count, blood chemistries, urinalysis, antinuclear antibodies, anti-dsDNA, VDRL, complement and immunglobulin levels, the search for ENA-5 antibodies (SS-A, SS-B, RNP, Sm, Scl-70, Jo-1), CRP, RF were normal or negative. There were slightly increased levels of an erythrocyte sedimentation rate of 35 mm/h.

Dermatopathologic examination showed a lymphocytic infiltrate extending to the level of the subcutaneous fat. There was fibrosis of the fat septate and extensive hyaline deposition within the fat lobules. Lymphoid aggregates, some showing germinal center formation, were present throughout the subcutaneous fat. Foci of calcification were also noted (Fig. 2). Direct immunoflorescence performed on normal-appearing skin showed granular and linear deposition of IgM and C3 along the basement membrane zone.

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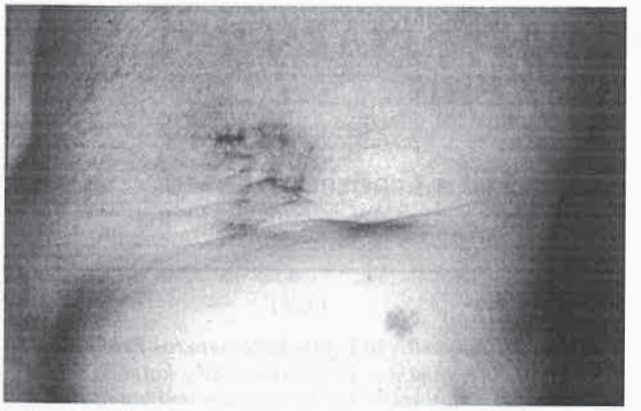

Figure 1: Irregular indurated, depressed plaques with tethered skin over the right hip.

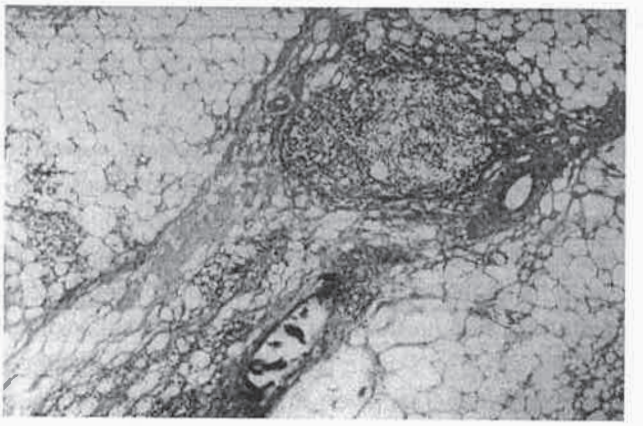

Figure 2: Lymphocytic panniculitis with hyaline necrosis of fat cells (H&E, X 400).

On the basis of these data, we diagnosed lupus erythematosus profundus. The patient was treated with Hydroxychloroquine (Plaquenil) at a dose of 200 mg twice daily for four weeks. She was subsequently maintained on 200 mg daily for an additional two months. There was complete regression on the inflammatory lesions, but she was left with residual subcutaneous atrophy at the sites of the involvement.

DISCUSSION

The finding of subcutaneous nodules in patients with LE was first reported by Kaposi in 1883 and was later termed lupus erythematosus profundus by Irgang in 1940. It is now usually referred to as Kaposi-Irgang disease. The term lupus panniculitis is used to describe lesions with exclusive involvement of the subcutaneous layers (2,5).

Clinically, the often-painful subcutaneous nodules, or plaques, show a predilection for proximal sites, and the overlying skin may be normal or have ulceration, hyperkeratosis or atrophy. After healing, they typically leave areas of depression and delling. Most patients who develop lupus profundus are between 20 and 60 years old, and women are affected more frequently than men (2-7). Thus, our patient, a 31-year-old female, fits this profile well.

There is a strong association of lupus profundus with discoid LE; discoid lesions are found in around 70% of patients with lupus panniculitis. Discoid lesions may develop either with the onset of lupus profundus or several years before or after the onset of lupus panniculitis. Laboratory findings of most patients include antinuclear antibodies, although usually at low titers, anti double-stranded DNA, anti-ENA-antibodies and hipocomplementemia. Leukopenia, false + VDRL and an increased ESR are common features (2-5). Our patient had no skin lesions resembling discoid LE, nor did she fulfill the ARA criteria for SLE.

In the differential diagnosis, various types of panniculitis, including morfea profunda, connective tissue panniculitis, Weber-Chiristian panniculitis, lipodystrophy and lymphoma should be considered. The exact pathophysiologic mechanism responsible for the production of lupus panniculitis is unknown at the present time. It is conceivable that the panniculitis associated with an overlying cutaneous lupus lesion may represent an extension of the inflammatory infiltrate from the dermis into the subcutaneous tissue. The panniculitis occurring in the total absence of an overlying cutaneous lesion may be the end result of a vasculopathy (2,3,5).

Treatment of lupus profundus is similar to that of discoid LE. Effective treatment using thalidomide, dapsone and the antimalarial drugs hydroxychloroquine, choloquine, quinacrine have been reported (5,8,9). Systemic corticosteroid treatment may be useful in the initial therapy of patients with extensive inflammation (2-4). Since trauma has been described as triggering some cases of LEP, surgical treatment should be considered only when other treatment modalities have failed and if the disease is debilitating (3). LEP has been reported in association with rheumatoid arthritis, Sjögren's syndrome, chronic ulcerative colitis, Hashimato's thyroiditis and thrombocytopenic purpura (2). To our knowledge, this is the first report of LEP associated with dermatomyositis in the literature.

As dermatomyositis in this patient was in complete remission and the relevant autoantibodies were negative, we consider this a coexistence rather than a continium of a mixed connective tissue disorder.

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SUPRATENTORIAL METASTASIS OF GLIOBLASTOME MULTIFORME TO THE PITUITARY STALK

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SUMMARY

Primary brain tumors rarely metastasize to localizations far from the primary site. Pituitary stalk metastasis is also a rarely encountered abnormality. Most of the reported pituitary stalk metastases are from the extracranial malignancies such as breast cancer and lung cancer. Here we present a case of pituitary stalk metastasis from the infratentorial glioblastome multiforme (GBM). A 17 year-old female patient had been operated on for a posterior fossa mass 8 months before admission, histopathologic examination of the mass had been reported as glioblastome multiforme. She had been traeted with radiotherapy and chemotherapy. On postoperative radiological evaluation eight monts later a pituitary stalk mesatstatic lesion was detected. Since patient did not have any symptoms and signs of the metastatic lesion, she did not undergo a surgical therapy. Extra course of chemotherapy was recommended. As far as we know, our case is the first in the literature reporting a pituitary stalk metastasis from an infratentorial GBM.

Key words: *Glioblastome multiforme, Metastasis, Pituitary stalk*

ÖZET

İnfatentoriyal Glioblastome Multiforme: Hipofize Metastaz

Primer beyin tümörleri seyrek olarak primer alandan uzak mesafelere metastaz yaparlar. Hipofiz bezi metastazı seyrek rastlanan bir patolojidir. Rapor edilmiş hipofiz bezi metastazlarının çoğu göğüs kanseri, akciğer kanseri gibi ekstrakranyal malignensilerden olmaktadır. Biz burada infratentoriyal glioblastome multiformenin hipofiz bezi metastazı olan olguyu sunuyoruz 17 yaşında bayan hasta bize başvurusundan 8 ay önce posterior fossa tümörü nedeniyle opere edilmiş ve kitlenin histopatolojik incelemesi glioblastome multiforme olarak gelmiş. Hasta ayrıca radyoterapi ve kemoterapi almış. Postoperatif 8. ayda yapılan radyolojik incelemede hipofiz bezi metastatik lezyonu belirlendi. Hastanın metastatik lezyona ait hiçbir semptom ve bulgusu olmadığı için hastaya cerrahi girişim uygulanmadı. Hastaya kemoterapi önerildi. Bizim bilgidimiz kadarıyla bu olgu litaratürde rapor edilen ilk infratentoriyal glioblastoma multiforme hipofiz bezi metastazıdır.

Anahtar Kelimeler: *Glioblastome multiforme, Metastaz, Hipofiz bezi*

Glial tumors don't metastasize frequently by the routes other than seeding. There are many reports about the seeding of glioblastoma multiforme and medulloblastoma to the distant localizations especially to the spinal cord, from the primary site. But extracranial metastasis, infratentorial to supratentorial or vice versa, were rarely reported (1). Some meningiomas also occasionally have been reported to metastasize to extracranial tissues (2). Metastasic pituitary tumors are rare but represent an important differential diagnosis of intrasellar tumor syndromes. Metastatic pituitary stalk tumors are even rather rare. In the literature, pituitary stalk metastasis have been reported only as case reports (2,3,4). They have some clinical and radiological characteristics necessitating a special handling. We present a case of pituitary stalk metastasis from an infratentorial glioblastome multiforme (GBM).

CASE REPORT

A 17 year - old female patient had been operated in our Neurosurgery Clinic with the diagnosis of right cerebellar mass lesion in February 1997. She had been operated on and mass lesion had been resected gross totally. Histopathologic examination of the lesion had been reported as GBM. In postoperative period he had been given 6000 cgy of radiation therapy and six courses of chemotherapy including Oncovine (vinblastin), CCNU, and procarbazine. On a routine control magnetic resonance imaging (MRI) in October 1997, there was no residual or regrowth of cerebellar tumor. But pituitary stalk was thick and hyperintense on T1W MRI sections (figure 1,2). It was reported as a metastatic lesion from the infratentorial glial tumor. Patient underwent ophthalmologic and endocrinologic evaluations, no abnormality was found including diabetes insipidus. Since she did not have any complaints regarding to the lesion she was not operated on, but she was given extra courses of chemotherapy. After two courses of chemotherapy patient lost follow up.

DISCUSSION

Brain tumors rarely metastasize. Metastasis generally occurs by seeding via cerebrospinal fluid. Haematogenous spread is not as frequent as seeding.

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GBM or medulloblastomas are frequently reported metastasizing by seeding through cerebrospinal fluid to the spinal cord. GBM and, rarely, meningioma cases were reported to metastasize to extracranial spaces (1,5). The most common sources reported, metastatic to the pituitary-hypothalamic region were breast, lung, and the lymphoma/leukemia group (2,6,7,8). Pituitary stalk metastasis from a GBM has never been reported before. Pituitary gland and stalk metastasis have the same clinical and radiological picture with the primary lesions of the gland (9). Clinically, pituitary stalk metastasis usually presents with the signs of diabetes insipidus (3). Large lesions may cause other hormonal imbalances and visual problems by compressing or infiltrating the chiasma, which are the similar characteristics with the primary tumors of the pituitary gland. Our case has no complaint related to the stalk metastasis.

The clinical and radiological features, which may evoke an intrasellar or stalk metastasis were: the tumorous syndrome associated with or revealed by diabetes insipidus. MRI appears to be the best procedure to perform, showing stalk thickening and homogenous enhancement after gadolinium injection (3, 7,10), and bilobar character of the mass which is in favour of rapid cell proliferation, postero-superior extension, lowering of the third ventricle floor and eventhough computerized tomography demonstrates the pituitary stalk thickening. Treatment of the metastatic pituitary stalk lesion depends on the clinical state of the patient. If the lesion causes metabolic changes i.e. diabetes insipidus, first medical treatment with DDAVP was tried if it fails decompressive resection of the lesion causes compression to the adjacent structures surgical decompression is the choice of treatment. Postoperative close follow up, for the diabetes insipidus development, is necessary. Recently some authors reported the resection of stalk lesions without damaging the pituitary gland (4,8,9).

This case is unique in that it is the first case in the literature reported as the metastasis of an infratentorial GBM to the pituitary stalk.

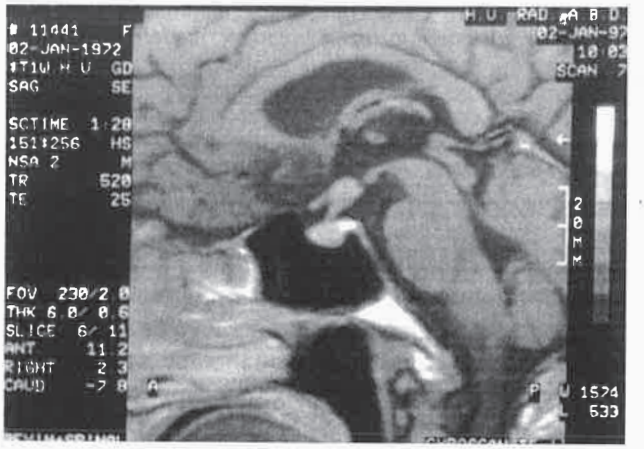

Figure 1: MRI sagittal section demonstrating the enhancing swollen pituitary stalk.

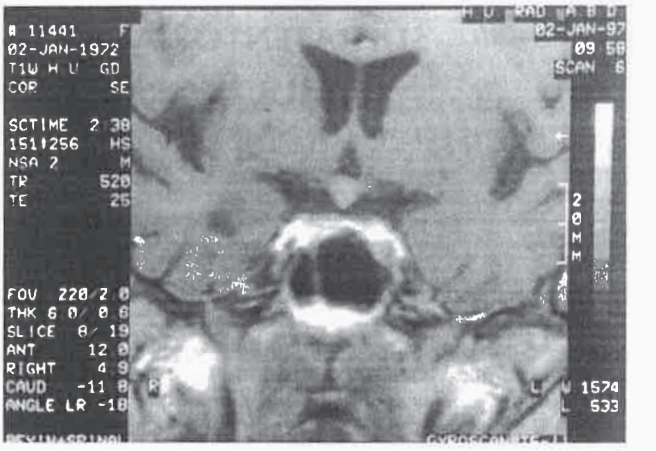

Figure 2: MRI Coronal view of the pituitary stalk metastasiss

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