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A COMPARISON BETWEEN RESTENOSIS RATES OF CONVENTIONAL ANGIOPLASTY AND STENT IMPLANTATION FOR CHRONIC CORONARY TOTAL OCCLUSIONS

Tamer Sayın* • Gülgün Pamir* • Derviş Oral* •Kenan Ömürlü* • Eralp Tutar* • Çetin Erol*
Ahmet Alpman* • Berkten Berkalp* • Celal Kervancıoğlu*

SUMMARY

Although it is well documented that coronary stents improve restenosis rates for stenotic lesions by randomized, large scale studies, there is yet few limited data comparing restenosis rates of chronic coronary total occlusion angioplasty and stent implantation. The present study aimed to compare the angiographic restenosis rates between conventional angioplasty and stent implantation for chronic coronary total occlusions. We also the investigated restenosis and reocclusion rates, respectively. In this study, we reviewed our registry between January 1987 and December 1997 retrospectively. Analysing the angiographic data we had two groups of patients who had control coronary angiograms 4-6 months after the initial procedure: PTCA group and the stent group. Patients, in whom TIMI III flow could be established were selected for follow up coronary angiography. In the stent group there were 50 patients, in the PTCA group we had 118 patients,121 lesions. Restenosis rates were 34 and 62 % respectively (p<0.01). Reocclusion rates were 6 % and 29.8 % (p= 0.002)

***Conclusion:** Stent implantation should be done whenever TIMI III flow could be established to improve angiographic restenosis rates of chronic coronary total occlusions.Reocclusion occurs far less frequently after stent implantation with respect to PTCA for chronic coronary total occlusions which may provide ease for a new revascularization attempt.Furthermore less restenosis and less reocclusion may improve left ventricular function.*

***Key words:** Stent, chronic total occlusion, angioplasty*

ÖZET

Kronik koroner total oklüzyonlarda konvansiyonel anjiyoplasti ile stent implantasyonun karşılaştırılması

Stent implantasyonu ile stenotik lezyonlarda konvansiyonel anjiyoplastiye göre restenoz oranının azaldığı randomize, geniş hasta populasyonlu çalışmalarla gösterildiği halde kronik koroner total oklüzyonlar için az sayıda veri mevcuttur. Bu çalışmada kronik total oklüzyonu olan hastalarda konvansiyonel anjiyoplasti uygulanan hastalarla stent implante edilen hastaların retrospektif olarak anjiokardiyografik restenoz oranları karşılaştırıldı. Kronik total oklüzyona girişim neticesinde TIMI III akım sağlanabilen hastalar takibe alındı. Retrospektif olarak Ocak 1987 ile Aralık 1997 tarihleri arasında anjiyografi laboratuarı kayıtları incelendi. Restenoz izlenen hastalarda restenoz ve reoklüzyon ayrı ayrı incelendi. Girişim yapılan ve 4-6 ay sonra anjiografik kontrolu olan hastalar çalışma grubunu oluşturdu. Kontrol anjiografisi olan hastalar PTCA ve Stent grubunu oluşturdular.Stent grubunda 50 hasta, PTCA grubunda ise 118 hasta 121 lezyon vardı. Restenoz oranları sırasıyla % 34 ve %62 (P<0.01), reoklüzyon oranları ise % 6 ve % 29.8 (P=0.002) olarak bulundu.

***Sonuç:** TIMI III akımın elde edilebildiği kronik koroner total oklüzyonlarda restenoz oranlarını azaltabilmek için stent implantasyonu yapılmalıdır. Restenozun şekli stent uygulanan hastalarda çok daha az olarak reoklüzyon şeklinde olmakta bu da daha sonra yapılabilecek revaskülarizasyon işlemini kolaylaştırmakta. Daha az restenoz ve daha az reoklüzyon ventrikül fonksiyonlarının düzelmesine yardımcı olabilir.*

***Anahtar kelimeler:** Stent, kronik total tıkanma, anjiyoplasti*

The first report on coronary occlusion angioplasty was published by Savage et al. in 1982 (1). Since then better survival rates were reported with successful chronic total occlusion (CTO) angioplasty with respect to failed procedures (2-4). A total occlusion that is well collateralized is functionally equivalent to a 90 % stenosis (5) that sustains viability but produces clinically apparent ischemia with increased oxygen demand. Relief of angina pectoris is reported 70 % on average in several studies (6-11). Another potential benefit

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with CTO angioplasty is that there is less need for subsequent coronary artery by-pass surgery after a successful procedure (3, 7, 11, 12). Also it has been reported that global and regional left ventricular function may improve after successful CTO angioplasty (13,14). Main limitation of CTO angioplasty is lower procedural success and higher restenosis rates (average 65 % and > 50 % respectively) (4). It has been shown, with randomized large scale studies that coronary stents improve restenosis rates for stenotic lesions (15,16). However there are few reports on stent implantation for CTO (17-19). In the present study we reviewed our angiographic data retrospectively to compare restenosis rates of PTCA and stent implantation for CTO. We also examined the reocclusion rates in the restenotic patients for both groups.

METHODS

We reviewed our registry between January 1987 and December 1997 retrospectively. We have performed 4250 angioplasty procedures and 994 stent implantation in the given period. Seven hundred and fifteen of the angioplasty procedures (16.8 %) and 170 of the stent implantation (17.1 %) was for CTO.

Patient Selection: A CTO was defined as an absolute lack of blood flow in the related coronary artery (TIMI 0 flow) with a duration of at least one month. Patients with "Functional Occlusions" (with TIMI I flow) were not included.The age of occlusion was estimated from clinical data (time of infarction or sudden increase of anginal symptoms) or from the date of previous angiogram (if available). Age of occlusion could be categorized as < 12 hours old acute, > 12 hours and< 1month old as subacute, > 1month and < 3 months as early chronic and > 3 months as late chronic (4). We selected patients with < 1month occlusions if ever it was possible to estimate regarding a clinical event or a coronary angiogram. Patients with reocclusion lesions related to a previous procedure were not included in this study.

The indication for an angioplasty procedure for both groups was clinical, angiographic or scintigrafic, evidence of ischemia in the territory of the related artery. All PTCA procedures were done using a moveable guide wire / dilatation system, with 0.014 inch wires and low profile dilatation catheters. All patients received intravenous 10000-15000 U of heparin at the beginning of the procedure; sublingual or intracoronary nitroglycerin was given as needed during the procedure. The indication for a stent employment was dissection, suboptimal result, elective or elastic recoil. Stents of different diameters (range 2.5-4 mm) and different types were used. Stents were either mounted to dilatation catheters with hand crimping or pre-mounted on a PTCA catheter. All patients were asked for a control coronary angiogram at 4-6 months. Patients treated with a PTCA procedure who also had a control coronary angiogram formed PTCA group. Patients treated with a PTCA and stent procedure and who had control coronary angiograms formed the stent group. It was essential that TIMI III flow should be established for the patients to be enrolled in the study. A successful procedure was defined as a final luminal diameter of 20 % or less in the related artery, with established TIMI III flow, without a major complication (death, emergency by-pass, acute miyocardial infarction). Restenosis was defined as 50 % or more narrowing of the luminal diameter. Angiocardiographic analysis was done with visual assessments of two experienced invasive cardiologists. After a successful stent employment three different protocols of antithrombositer-anticoagulant theraphy was used. For those with perfect result protocol A was preferred. Protocol A consisted of five days of combined ticlopidine and aspirin therapy, continued with a 25 days of ticlopidine alone and then with aspirin consistently. Protocols B and C were preferred when there was doubt for possible thrombus or residual dissection. Protocol B consisted of 7-10 days of 2 x 0.1 ml / 10 kg of sc low molecular weight heparin in addition to protocol A. Protocol C consisted of 2 days of heparin infusion therapy (ACT levels 200-250 second) in addition to protocol B. For the majority of the stent patients (76 %) we used protocol A.

RESULTS

We have performed 885 CTO angioplasty procedures in the given period and 19.2 % of the lesions have been stented. Success rate for total occlusion angioplasty was 64.9 %. For PTCA patients 138 of them had control coronary angiograms (29.7 % of the successful PTCA procedures). Of that 138 patients 118 patients (121 lesions) fullfilled patient selection criteria and formed PTCA group. Sixty three of the patients with implanted stents for a total occlusion had control coronary angiogarams (37 %) and 50 of them fullfilled inclusion criteria and formed the stent group. There were 9 women and 109 men in the PTCA group aged 51.2 ± 8.6. In the stent group there were 7 women and 43 men aged 49.6 ± 8.6.

For the 50 stent patients 2.5 mm diameter stents were used in 11 patients, 3.0 mm stents were used in 32 of the patients, 3.5 mm stents were used in 6 patients and 4 mm stent in one patient.

Complication rates for the whole of the total occlusion PTCA patients (715 patients) were as follows: Four patients died (0.6 %). One due to left main coronary dissection, one due to cardiac tamponade, one due to left ventricular failure after the procedure, one due to sudden death 9 days after the procedure. Two patients had completely reversible cerebral accidents (0.3 %). One had reversible facial paralysis, the other had transient ischemieac attack. One patient had an inguinal hematom requiring transfusion (0.1 %). Two patients had coronary ruptures; one given to emergency surgery, the other could be treated conservatively (0.3 %). One patient was given to emergency bypass surgery because of a left main dissection, with the other patient treated with emergency by-pass operation for coronary rupture giving the emergency operation ratio 0.3 % . One patient had MI (0.1 %).

In the whole stent group for total occlusions (170 patients) one patient died following a MI (0.6 %). Four had MI (% 2.4) and one had transfusion requiring inguinal hematom (0.6 %).

In the PTCA group three patients were treated for their 2 occlusive coronaries in the same attempt. When comparing restenosis rates, for PTCA group 75 of 121 lesions (62 %) and for stent group 17 of 50 patients (34%) were found to have restenotic lesions with control coronary angiograms ($p< 0.01$) (Table 1). When the statistical analysis for angiographic restenosis rates between the 2 groups was done we noted a significant advantage ($p<0.01$) in favour of stent group.

We also investigated the nature of restenosis with respect to the stent and PTCA groups. We found that PTCA patients had reocclusions more frequently than stent patients. Thirty six of 121 PTCA lesions had reocclusions (29.8%) while 3 of 50 patients had reocclusions (6%) (Table 2).

We also investigated the indications of stent deployment and looked for restenosis relationship.Twenty five of 50 were deployed because of dissection, 20 because of a suboptimal result or elastic recoil and five of them electively. There was no statistical significance with respect to restenosis rates.

Table 1. Restenosis rates of PTCA and Stent groups

	PTCA	Stent	P value
Total no. Of Lesions	121	50	
Restenosis (+)	75 (62%)	17 (34%)	<0.01

Table 2. Number of reocclusions in PTCA and Stent groups

	PTCA	STENT	P Value
Total no. Of Lesions	121	50	
Reocclusion (+)	36 (29.8%)	3 (6%)	0.002

DISSCUSSION

It is well documented that stents improve angiographic restenosis rates for stenotic lesions. Probably they also do the same for occlusive lesions. In the previous studies about 20 % restenosis rates were reported (17,18). In the first randomized study authors found significant statistical advantage in terms of restenosis rates with respect to PTCA alone (19).

In our study group, checking carefully for chronic total occlusion angioplasty patients we could find 118 patients (121 lesions) who fullfilled patient selection criteria. Those patients had TIMI III flow at the end of the procedure and they had control coronary angiograms (PTCA group). In the stent group there were 50 patients with TIMI III flow at the end of their procedure and they also had control coronary angiograms. Comparing the PTCA group with respect to stent group in terms of restenosis and reocclusion we found 62 % and 34 % restenosis rates ($p<0.02$) and 29.8 % and 6 % reocclusion rates ($p=0.002$) respectively. Our findings were quite paralell to reported studies up to date (17, 18, 19).

As a limitation of the present study we need to mention that we do not have detailed clinical information for the PTCA and stent groups (incidence of hypertension, diabetes, cigaratte smoking, lipid profile). Cumulation of one or more of these risk factors might have affeccted the results.

We also, like the other researchers (18, 19) concluded that stent implantation after recanalysing a CTO significantly reduces restenosis rates if TIMI III flow could be established. We calculated 62 % restenosis rate in the PTCA group versus 34 % in the stent group. There may be several mechanisms explaining this benefit including more acute luminal gain with stent deployment, scaffolding effect of stents providing a smooth border and possibly reducing early elastic recoil or late vessel remodelling. Probably the most important of these factors is more acute luminal gain with a stent deployment. Goldberg et al (17) found

that after PTCA of a total occlusion although the angiocardiographic outlook seemed satisfactory they could still have some more luminal gain with a stent deployment by using intravascular ultrasound in some of their patients. Also in SICCO study (19) postprocedural minimal lumen diameter was significantly higher in the stent group.

In our study we also compared nature of the restenotic lesions. We concluded that reocclusion occured significantly less with stent implantation, 29.8 % in the PTCA group versus 6 % in the stent group. The SICCO group (19) also reported less reocclusion but it did not reach statistical significance. Goldberg et al (17), in their 59 patients with a CTO stented reported a restenosis rate of 20 % with only one reocclusion which also favors less reocclusion with stent implantation. This point, non-occlusive restenosis also seems important not only because of possible improvement in wall motion abnormalities (14, 20, 21) but also it gives the patient the chance of another revascularization attempt.

The present study, a non randomised, retrospective, observational one lacks some of the clinical characteristics of the patients and rather focus on angiographic data. Such limitations are inherent for retrospective studies however they still are undoubtedlly valueable because they provide more information for cumulative data and metaanalysis.

CONCLUSION

Stent implantation for a chronic coronary total occlusion improves angiographic restenosis rates with respect to PTCA. Stent implantation should be done if a CTO could be recanalyzed to have TIMI III flow, also elective implantation should be done more frequently as stents reduce restenosis rates. Stent implantation causes significantly less reocclusion giving the patient the chance of a new revascularization attempt, possibly improvement in left ventricular function. This makes another reason for stent implantation for patients with CTO.

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HEART RATE VARIABILITY: A NON-INVASIVE MARKER OF SUSCEPTIBILITY TO VENTRICULAR TACHYCARDIA INDUCTDION

Oben Döven* • Muharrem Güldal* • Remzi Karaoğuz* •Ömer Akyürek*
Tamer Sayın* • Derviş Oral*

SUMMARY

Aim:This study examines the relation between heart rate variability (HRV) and the inducibility of ventricular tachycardia (VT) in 50 patients with cardiovascular disease.

Methods and results:*HRV data were collected using 24-hour ambulatory electrocardiogram in patients who consecutively underwent electrophysiologic testing. The mean age of the patients was 51.10±13.14 years (±SD) and the mean ejection fraction was 0.45 ± 0.16 . In 26 patients in whom sustained , monomorphic VT was inducible by programmed ventricular stimulation, mean R-R interval (mean RR), its standard deviation (SDNN), 5 minutes segments analysis (SDNN-i:mean of the 5 minute RR SDs and SDANN-i: SD of the 5-minute mean RR intervals), mean squared successive difference (MSSD) and percentage of cycles differing from the preceding one by more than 50 msec (pNN50) was significantly different than in the 24 patients in whom VT was not inducible (85.7±30.4 msec vs 134.2±40.9 msec, 41.5±20.8 msec vs 76.7±54.3 msec, 68.6±25.3 msec vs 110.8±36.5 msec, 38.5±26.2 msec vs 65.3±33.7 msec and 6.8±4.3 % vs 12.5± .1%). The patients who had inducible VT did not differ significantly from those who did not with regard to gender, RR interval and VES/24-hours. Reduced HRV was found to be well associated with VT inducibility.*

Conclusion: *HRV parameter may be helpful in predicting which patients are and are not likely to have inducible VT by programmed stimulation.*

Key words: *Heart rale variability- Ventricular tachycardia*

ÖZET

Ventriküler Taşikardi İndüksiyonunda Kalp Hızı Değişkenliğinin Non-invazif Gösterge Olarak Kullanılması

Amaç: *Kardiyovasküler sistem hastalığı olan 50 hastada kalp hızı değişkenliğinin (KHD) ventriküler taşikardi indüklenmesindeki tanısal değeri araştırılmıştır.*

Gereç ve Yöntem: Elektrofizyoloji laboratuarında programlanmış ventriküler stimülasyon planlanan 50 hastadan prospektif olarak 24 saatlik kalp hızı değişkenliği analizleri alındı. Hasta grubunun 24'ünde koroner arter hastalığı, 7'sinde dilate kardiyomiyopati, 6'sında hipertansiyon, 5'inde romatizmal kalp kapak hastalığı ve 3'ünde de mitral kapak prolapsusu mevcuttu. 38 erkek ve 12 kadından oluşan hasta grubunun ortalama yaşı 51.1±13.1 yıl, ortalama ejeksiyon fraksiyonu ise 0.45±0.16 olarak hesaplandı.

Bulgular: *Hastaların 26'sında programlanmış ventriküler stimülasyon ile kalıcı monomorfik ventriküler taşikardi (VT) atağı indüklendi. VT indüklenen hasta grubunda KHD parametrelerinden 24 saatlik kayıttaki RR intervallerininin standart sapmaları (SDNN: 85.7±30.4 ms; 134.2±40.9 ms), 5'er dakikalık periyotlardaki RR intervallerinin standart sapmalarının ortalamaları (SDNN-i: 41.5±20.8 ms; 76.7±54.3 ms), 5'er dakikalık periyotlardaki RR intervalleri ortalamalarının standart sapmaları (SDANN-i: 68.6±25.3 ms; 110.8±36.5 ms), 24 saatlik Holter kaydında 50 ms'den uzun interval farkı gösteren interval sayısının toplam RR interval sayısına olan oranı (%pNN50: 6.8±4.3 %; 12.5± .1%).) ve ardışık RR interval farklarının kareleri ortalamasının karekökleri (r-MSSD: 38.5±26.2 ms; 65.3±33.7 ms) VT indüklenmeyen hasta grubuna göre anlamlı olarak farklı bulundu. VT indüklenen ve indüklenmeye hasta grupları arasında cinsiyet, ortalama RR intervalleri ve 24 saatlik ventriküler ekstrasistol sayıları arasında anlamlı fark gözlenmezken kalp hızı değişkenliği parametrelerinde her iki grup arasında önemli fark gözlendi (p<0.05).*

Sonuç: *Ventriküler taşikardi indüklenmesinde 24 saatik kalp hızı değişkenliği parametrelerinin tanısal değere sahip olduğu sonucuna varıldı.*

Anahtar kelimeler: *Kalp hızı değişkenliği, ventriküler taşikardi*

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Sudden cardiac death represents 40% of the total deaths due to cardiovascular disease. Ventricular fibrillation without myocardial infarction is the major etiologic factor for these cardiac arrest events. (1,2)

The last two decades have witnessed the recognition of significant relationship between autonomic nervous system and cardiovascular events.(3,4) Increased sympathetic or reduced vagal activity associate with lethal arrhythmias so that efforts are given for the development of quantitative markers of autonomic activity. (5)

Heart rate variability (HRV) represents one of the most promising such markers. Many different parameters of HRV are more complex than generally appreciated. Combination with other techniques may improve the diagnostic accuracy of this test.

The purpose of the current study was to evaluate the predictive value of HRV in inducibility of VT in patients with high risk of sudden cardiac death.

METHOD

Patient population: The study population consisted of 50 patients who was referred for programmed ventricular stimulation test protocol between February 1997 and July 1998. Patients with atrial fibrillation, acute myocardial infarction and unstable angina pectoris were not included in the study. We performed 24 hours Holter monitoring, 24 hours HRV, and echocardiographic evaluation before the electrophysiologic study. Ambulatory twenty-four-hour electrocardiogram: Two-channel 24-hour Holter recordings were recorded from all the subjects and analyzed with a Medilog Excel (version 4.1c., Oxford Medical Ltd) ECG software system.

Heart rate variability index: ECG data were sampled digitally from the Oxford Medilog scanner for analysis of HRV. The computer program automatically calculates all 24 hour RR interval series. Premature atrial and ventricular beats and the subsequent interval were excluded automatically by the analysis, and the automatic detection was also visually checked by the investigator for proper identification.

Time domain variables considered in this study were mean R-R interval (mean RR), its standard deviation (SDNN), 5 minutes segments analysis (SDNN-i:mean of the 5 minute RR SDs and SDANN-i: SD of the 5-minute mean RR intervals), mean squared successive difference (MSSD) and percentage of cycles differing from the preceding one by more than 50 msec (pNN50).

The electrophysiological testing included incremental ventricular pacing and programmed ventricular stimulation using up to three extrastimuli at two basic drive cycle lengths (600 and 400 msec) from the right ventricular apex and outflow tract. VT was defined as sustained when its duration was >30 seconds.

Statistical analysis: The results were analyzed with the statistical package for social sciences. Continuos variables are presented as mean ±SD. The significance of changes were done by Student's t test, Mann Whitney U test, variance analysis, correlation analysis and logistic regression analysis. A value of $p<0.05$ was regarded as a significant.

Results

Study population: 50 patients were included in the analysis. Mean age was 51.10 ±13.14 (38 male and 12 female). 24 patients had coronary artery disease (CAD), 7 had dilated cardiomyopathy (DCMP) and 3 had mitral valve prolapsus (MVP). Underlying organic heart disease was not found in 5 patients. In presentation, 11 patients had syncope, 7 had documented non-sustained VT, 17 had sustained VT, 8 had resuscitated cardiac arrest. Remaining 7 patients had symptoms of palpitation episodes with frequent documented ventricular extrasystoles.

Mean heart rate of patients was 72.2±14.3. The averaged ejection fraction of the patients was 44.7±16.8 (range of 19.0 to 70.0 %). All patients we-

Table 1. Diagnosis of patient population

	n (number)	%
Coronary artery disease	24	48.0
Hypertension	6	12.0
Idiopathic DCMP	7	12.0
Rheumatic heart disease	5	10.0
Mitral valve prolapsus	3	6.0
No Underlying disease	5	10.0

Table 2. Clinical profile of study population

	n (number)	%
Syncope	11	22.0
Nonsustained VT	7	14.0
Sustained VT	17	34.0
Sudden cardiac arrest	8	16.0
Palpitation	7	14.0

re administered 1 or more antiarrhythmic medications. They all were on medication while wearing Holter monitor. Of these 50, 10 were taking class I, 7 were taking class II, 30 were taking class III, and and 12 were taking class IV antiarrhythmic drugs. The averaged number of antiarrhythmic medications per person was 1.2.

We divided the patients in two groups according to the VT induction with electrophysiological testing. VT induced group, Group I was consisted of 26 patients. Group II , VT non-induced group were 24 patients. In VT induced group age was older and EF was lower than the non-induced group. Even though sex, mean heart rate and number of VES in Holter monitoring were not different between the two groups, HRV parameters (SDNN, SDNN-i, SDANN-i, r-MSSD and pNN50%) differed significantly with statistical analysis.

Ejection fraction is one of the most important prognostic criteria in patients with cardiovascular disease. There was also significant correlation of SDNN (r: 0,4853), SDNN-i (r: 0,3918) and SDANN-i (r: 0,4988) with ejection fraction in study population.

When we apply the risk analysis to HRV parameters for VT induction in laboratory. We found that SDNN < 72.3 msec increases VT induction risk 11.2 times, SDNN-i <54.5 msec increases risk 19.9 times, pNN50% <5.57% increases the risk of VT induction 8.1 times.

Table 3. Clinical, Holter and HRV characteristics of patients in VT inducible and non-inducible groups

	Group I (n=26; 52%)	Group II (n=24; 48%)	p
Sex (male)	21 (80.7%)	17 (70.8%)	NS
Age	57.4±12.6	44.7±15.3	<0.01
EF %	34.8±12.6	55.6±11.8	<0.001
Holter(VES/24 h)	2422±2557	1976±2624	NS
Mean heart rate	71.1±12.9	73.9±16.7	NS
Mean RR	925.2±150.6	838.8±182.1	NS
SDNN	85.7±30.4	134.2±40.9	<0.001
SDNN-i	41.3±20.8	76.7±54.3	<0.05
SDANN-i	68.6±25.3	110.8±36.5	<0.001
MSSD	38,5±26.2	65.3±32.7	<0.05
pNN50%	6.8±4.3	12.5±7.1	<0.05

NS: Nonspecific
SDNN: 5 minutes segments analysis
SDNN-i: Mean of the 5 minute RR SDs
SDANN-i: SD of the 5-minute mean RR intervals
MSSD: Mean squared successive difference
pNN50: percentage of cycles differing from the preceding one by more than 50 msec

Table 4. Correlation analysis of ejection fraction with HRV parameters

	EF	p
SDNN	r: 0.4853	<0.01
SDNN-i	r: 0.3918	<0.05
SDANN-i	r: 0.4988	<0.01
RMSSD	r: 0.2643	NS
pNN50%	r: 0.2168	NS

SDNN: 5 minutes segments analysis
SDNN-i: Mean of the 5 minute RR SDKs
SDANN-i: SD of the 5-minute mean RR intervals
MSSD: Mean squared successive difference
pNN50: Percentage of cycles differing from the preceding one by more than 50 msec

In VT induction, sensitivity of HRV parameters changed between the 63.6 % and 88.8 %, the specificity of the same parameter were between the 58.3% and 80.0 %. Among the different HRV parameters, SDNN-i (<54.5) had the highest validity index with 83.3% sensitivity and 80.0 % specificity. The cut off values were calculated from the non-induced group with formula of $x \pm t\ 0.95 * SD$.

Discussion

In the present study, the different parameters obtained from 24 hour HRV was shown to be well correlated with sustained VT induction by programmed stimulation protocol in electrophysiology laboratory. Reduced HRV was found to be well associated with low ejection fraction. It was also shown that beat-to-beat changes of heart rate together with the ejection fraction can be used for prediction of arrhythmia induction.

The mechanism by which the pathophysiological changes reflected by impaired HRV predisposes to the occurrence of malignant arrhythmias are largely unknown. Depressed HRV can also be used as a predictor of risk after acute MI and as an early warning sign of diabetic neuropathy.(6,7,8,9,10,11)

The data suggest that depressed HRV is not simple reflection of sympathetic overdrive due to poor ventricular performance but that is also reflects depressed vagal activity, which has a strong association with the pathogenesis of ventricular arrhythmias and sudden cardiac death.(12.13)

The predictive value of HRV alone is thought to be modest. Combination with other techniques substantially improves the positive predictive accuracy of HRV over a clinically important range of sensitivity

Table 5. Risk analysis of non-invasive parameters for VT inducibility in study population

	x^2	p	RR
Sex			
F	.....	.....	.....
M	1.87	>0.05	2.83
Age			
<40	.....	.....	.....
40-60	4.38	<0.05	11.24
>60	5.79	<0.05	16.66
EF %			
=>30	.....	.....	.....
<30	3.34	<0.05	5.18
SDNN (ms)			
=>72.3	.....	.....	.....
<72.3	4.50	<0.05	11.2
SDNN-i (ms)			
=>54.5	.....	.....	.....
<54.5	10.9	<0.001	19.9
SDANN-i (ms)			
=>99.2	.....	.....	.....
<99.2	3.33	>0.05	3.9
MSSD (ms)			
=>47.9	.....	.....	.....
<47.9	2.12	>0.05	3.0
pNN50%			
=>5.57	.....	.....	.....
<5.57	5.47	<0.05	8.1

EF: Ejection fraction
SDNN: 5 minutes segments analysis
SDNN-i: Mean of the 5 minute RR SDs
SDANN-i: SD of the 5-minute mean RR intervals
MSSD: Mean squared successive difference
pNN50: percentage of cycles differing from the preceding one by more than 50 msec

(25% to 75%) for cardiac mortality and arrhythmic events. Improvements of the positive predictive accuracy over the range of sensitivities have been reported for combinations of HRV with mean heart rate, left ventricular ejection fraction, frequency of ventricular ectopic activity, parameter of high resolution ECG (presence or absence of late potentials), and clinical assessment. (14,15,16) However, it is not known which other stratification factors are most feasible to be combined with HRV multifactoriel risk stratification.

Table 6. Diagnostic value of HRV parameters in VT induction with 95 % confidence interval

HRV parameters	Sensitivity %	Specificity %
SDNN (< 72.3 ms)	88.8	58.3
SDNN-i (<54.5 ms)	83.3	80.0
SDANN-i (<99.2 ms)	68.4	64.2
MSSD (<47.9 ms)	63.6	63.6
pNN50% (<5.57)	83.3	61.9

SDNN: 5 minutes segments analysis
SDNN-i: Mean of the 5 minute RR SDs
SDANN-i: SD of the 5-minute mean RR intervals
MSSD: Mean squared successive difference
pNN50: percentage of cycles differing from the preceding one by more than 50 msec

In this study, different time domain HRV parameter had relatively good sensitivities (63.3 % to 88.8%) and specificity's (58.3% to 80.0%). Among these parameters SDNN-i had the best diagnostic accuracy (sensitivity ; 83.3%, specificity; 80.0%) in VT induction.

In conclusion, HRV has considerable potential to asses the role of autonomic nervous system fluctuations in patients with various cardiovascular disorders and it has high sensitivity and specificity in inducibility of VT. It is also shown that, HRV is clinically useful adjunct when used with left ventricular ejection fraction.

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LEFT VENTRICULAR DIASTOLIC FILLING: DOES IT CHANGE DURING THE MENSTRUAL CYCLE IN HEALTHY WOMEN?

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SUMMARY

Diastolic left ventricular function is routinely assessed by Doppler echocardiography. In this study, the probable changes in diastolic filling pattern which were affected by fluid balance in the body, were searched during the menstrual cycle in healthy women. The study population consisted 33 healthy women who have regular menstrual cycle and used no oral contraseptive agent. Each women was evaluated by Doppler echocardiography at the 5th,14th ,21st , and 28th days of the menstrual cycle. Peak early diastolic filling wave (E) velocity, peak atrial diastolic filling wave (A) velocity, E/A ratio, deceleration time of E , time of E velocity, time of A velocity, total time of diastole, isovolumetric relaxation time, A velocity time integral, E velocity time integral, total velocity time integral, atrial filling fraction were measured by Doppler echocardiography. Blood pressure, heart rate, and body weight of the subjects were determined at each evaluation. In the study, mean age was 31±6 (range 21-41). Left ventricular dimensions, wall thicknesses, and systolic functions were normal. A decrease in E velocity time integral, atrial filling fraction, isovolumetric relaxation time, and in deceleration time of E were observed in luteal phase, but the differences were not statistically significant. Also no significant difference was demonstrated in peak early diastolic filling wave (E) velocity, peak atrial diastolic filling wave (A) velocity, E/A ratio, time of E velocity, time of A velocity, total time of diastole, A velocity time integral, total velocity time integral at the days of the 5th,14th ,21st , and 28th of the menstrual cycle of the women examined . In conclusion, the results of this study showed that the left ventricular diastolic filling is not affected in healthy women during the menstrual cycle.

Key words: *Pulsed doppler, diastolic filling, healthy subjects, female, menstrual cycle*

ÖZET

Sol ventrikül diastolik solunum: Sağlıklı kadınlarda menstrüasyonda değişiyor mu?

Sol ventrikül fonksiyonları Doppler ekokardiyografi ile rutin olarak değerlendirilebilmektedir. Bu çalışmada sağlıklı kadınlarda vücüdun sıvı dengesinden etkilendiği bilinen sol ventrikül diyastolik doluşundaki olası değişiklikler menstrüel siklus boyunca değerlendirildi. Çalışma grubu düzenli menstrüel siklusu olan, oral kontraseptif kullanmayan 33 sağlıklı kadından oluşmaktaydı. Çalışma grubu bireyleri menstrüel siklusların 5, 14, 21 ve 28. Günlerinde Doppler ekokardiyografi ile değerlendirildi. Doppler ekokardiyografide pik erken diyastolik doluş dalgası(E), pik atriyal diyastolik doluş dalgası(A), E/A oranı, E'ni' deselerasyon zamanı, E ve A'nın süreleri, total diyastol süresi, izovolumetrik relaksasyon zamanı, E ve A'nın hız-zaman integrali, total hız-zaman integrali ve atriyal doluş oranı ölçüldü. Her inceleme sırasında ayrıca kan basıncı, kalp hızı ve vücut ağırlıkları ölçüldü. Çalışmada ortalama yaş 31±6 yıl(21-41) bulundu. Sol ventrikül boyutları, duvar kalınlıkları ve sistolik fonksiyonları normal bulundu. Luteal fazda E'nin hız-zaman integrali, atriyal doluş oranı, izovolumetrik relaksasyon zamanı ve E'nin deselerasyon zamanında azalma saptandı, ancak fark istatistiksel olarak anlamlı değildi. Ayrıca pik erken doluş dalga hızı(E), pik atriyal doluş dalga hızı(A), E/A oranı, E ve A'nın süresi ve total diyastol süresi, A'nın hız-zaman integrali, total hız zaman integrali açısından incelemenin yapıldığı 5,14,21 ve 28. günlerde anlamlı fark saptanmadı. Sonuç olarak bu çalışmada sağlıklı kadınlarda sol ventrikül diyastolik doluşunun menstrüel siklus boyunca değişiklik göstermediği saptandı.

Anahtar kelimeler: *"Pulsed Doppler", diyastolik doluş, sağlıklı insan, kadın, menstrüel siklus*

Doppler echocardiography has proven increasingly useful as a noninvasive method for characterizing alterations in diastolic properties of the heart (1). Left ventricular filling not only reflects the diastolic properties of the left ventricle, but also hemodynamic factors, such as preload and afterload (2,3). In this study, the probable changes in diastolic filling pattern which were affected by fluid balance in the body, we-

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re searched during the menstrual cycle in healthy women.

METHODS

Study population: The study population consisted 33 healthy women who have regular menstrual cycle and used no oral contraseptive agent. All subjects were free of heart disease according to the following criteria: (1) no history of cardiovascular or any other chronic disease, (2) normal findings on physical examination, (3) normal 12-lead electrocardiogram, (4) normal findings on both M-mode, 2-dimensional and Doppler echocardiography, (5) no use of regular medication.

The resting blood pressure, heart rate, and body weight of the subjects were determined at each echocardiographic evaluation.

Echocardiography: Subjects were examined by M-mode, 2-dimensional, continuous and pulsed wave Doppler on a Toshiba (140 A, 3.75 MHz transducer) ultrasound machine. Each women was evaluated by Doppler echocardiography at the 5^{th},14^{th} ,21^{st} , and 28^{th} days of the menstrual cycle. Doppler examination of left ventricle inflow was performed from the apical 4-chamber view with the sample volume placed between the mitral leaflet tips. The ultrasound beam was lined up parallel to left ventricle inflow to minimize the angle of the cosine. Peak early diastolic filling wave (E) velocity, peak atrial diastolic filling wave (A) velocity, and the ratio of peak early to late velocities (E/A) were measured.

Deceleration time of E were calculated as the time from E to the time when the descent of E intercepted the zero line (4). Furthermore, time of E velocity, time of A velocity, and total time of diastole were also measured. Time velocity integral E and A, and total velocity time integral were assessed. Atrial filling fraction was measured as the ratio of the integral of the A wave to the total diastolic integral of the transmitral flow. The isovolumetric relaxation time was defined as the interval from end of the aortic flow to the the onset of the mitral flow.

Statistical analyses: Analysis of the data were performed using SPSS statistical software. All variables were expressed as mean ± SD. The echocardiographic data were collected on every 4 days were analysed by Friedman test. A p value < 0.05 was considered statistically significant.

RESULTS

Data were obtained from 33 healthy women; their ages ranged from 21 to 41 years (mean 31±6). All subjects had normal electrocardiograms at rest. Left ventricular dimensions, wall thicknesses, and systolic functions were normal. There were no statistical differences in body weight, heart rate, systolic and diastolic blood pressure measured at the days of the 5^{th},14^{th}, 21^{st}, and 28^{th} of the menstrual cycle of the women examined (Table 1).

A decrease in E velocity time integral, atrial filling fraction, isovolumetric relaxation time, and in deceleration time of E were observed in luteal phase, but the differences were not statistically significant. Also no significant difference was demonstrated in peak early diastolic filling wave (E) velocity, peak atrial diastolic filling wave (A) velocity, E/A ratio, time of E velocity, time of A velocity, total time of diastole, A velocity time integral, total velocity time integral at the days of the 5^{th}, 14^{th}, 21^{st}, and 28^{th} of the menstrual cycle of the women examined (Table 2).

DISCUSSION

There has been increasing interest in the use of Doppler echocardiographic indices of transmitral blood flow for the evaluation of left ventricular diastolic function. Left ventricular diastolic filling is in part affected by the diastolic properties of left ventricle (5). Also, other important factors may play a role in determining left ventricular filling; among them preload has been demonstrated to be one of the major determinants of the Doppler mitral flow velocity pattern (6,7). In the present study, we evaluated the effects of preload changes on the Doppler transmitral flow pattern in healthy women who had regular menstrual cycle. Est-

Table 1. Comparisons of demographic characteristics of healthy women during the menstrual cycle

	days of menstrual cycle			
	5^{th}	14^{th}	21^{st}	28^{th}
Body weight(kg)	59±9	59±9	59±9	60±9
Heart rate (/min)	81±9	84±8	84±11	82±11
SBP (mmHg)	111±12	122±14	119±17	113±16
DBP (mmHg)	72±10	73±7	74±7	73±10

All values were expressed as mean ± SD, P>0,05. SBP= systolic blood pressure, DBP= diastolic blood pressure.

Table 2. Comparisons of left ventricular filling characteristics of healthy women during the menstrual cycle

	Days of menstrual cycle			
	5th	14th	21st	28th
Peak E velocity(cm/s)	64±12	69±15	66±11	70±14
E velocity time integral (cm)	8±2	8±2	7±2	7±2
Time of E velocity(ms)	223±14	221±21	235±80	218±26
Deceleration time of E velocity(ms)	127± 23	123± 22	116± 21	117 ±20
Peak A velocity (cm/s)	54±9	55±11	55±10	55±9
A velocity time integral (cm)	4±1	4±1	4±1	4±1
Time of A velocity(ms)	158± 21	150± 20	150± 21	146 ±17
E/A velocity ratio	1.34± 0.2	1.28± 0.2	1.23 ±0.2	1.28± 0.2
Atrial filling fraction(%)	34± 8	33 ±5	32± 6	32 ±7
Total time of diastole(ms)	426± 76	417± 56	435± 108	429± 73
Total diastolic velocity time integral(cm)	12± 3	12± 2	12 ±3	11± 4
Isovolumetric relaxation time(ms)	75± 12	77± 9	75± 11	71± 8

All values were expressed as mean ±SD, p>0,05.

rogens cause some degree of salt and water retention. Normal women retain salt and water and gain weight just before menstruation (8). Our hypothesis is that on the different days of normal menstrual cycle such fluid balance changes could affect left ventricular diastolic filling.

Predictable changes in the patterns of the mitral velocity curves have been demonstrated in human differing loading conditions (9,10). It has been suggested that a reduction in preload can induce changes in Doppler transmitral flow pattern similar to observed in diastolic dysfunction (9,11). Choong et al used nitroglyserin infusion to decrease preload in a group of patients with various cardiovascular diseases; after nitroglyserin infusion, they observed a decrease in peak velocity and velocity- time integral of the E wave and in the total time velocity integral of the transmitral flow. No changes were observed in the peak velocity and velocity time integral of A wave (9). On the other hand, it was shown that preload increased by infusion of fluids resulted in a significant increase in E velocity and shortening of the deceleration time (12). Salt and water is retained in healthy women in luteal phase and as the menstruation begins, normal status is restored. Therefore, in the luteal phase, an increase of the mitral flow early rapid filling indices, and in the follicular phase a return to original values may be expected. In our study, in the luteal phase of the menstrual cycle, a decrease in deceleration time of E and isovolumetric relaxation time were shown but the differences were not statistically significant. Besides this, contrary to our expectations, in the luteal phase of menstrual cycle, E velocity time integral, E/A ratio, and atrial filling fraction decreased (not statistically significant). It was noticed that, the follicular and the luteal phases did not show observable differences for the other parameters studied. In the luteal phase of the menstruation, weigth gain was observed, however it was not statistically significant which may explain the lack of expected changes in the diastolic filling parameters.

In the study group, deceleration time of E is found to be low, especially at the 21st day of menstruation. The study group was formed with healthy subjects having no complains, with normal findings of physical examination, electrocardiogram and echocardiogram. Thus, observed short time of deceleration is unlikely to be due to the severe left ventricular dysfunction or restrictive type of left ventricular diastolic filling defect. In addition, although the deceleration time of E is short, the ratio of E/A and isvolumetric relaxation time were not in accordance with restrictive type of left ventricular diastolic filling defect.

Since mitral flow pattern is affected from variables such as heart rate (13) and afterload (14), the heart rate and the blood pressure were both measured din every echocardiographic examination. These variables did not change in the follicular and luteal phases.

In the previous three studies focusing on adult patient, transmitral Doppler parameters between men and women were compared, there were no significant differences (15,16, 17). Furthermore, in a study, it was reported that sex had a significant effect in subjects aged 40 to 60 years and this difference was assumed to be menopause related (18).

In our study, the left ventricular diastolic filling indexes did not show meaningful differences at the 5th, 14th, 21st, and 28th days of the menstrual cyles of the healthy women. In conclusion, the results of this study showed that the left ventricular diastolic filling is not affected in healthy women during their menstrual cycles.

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CLINICAL AND LABORATORY EFFECTS OF ALPHA INTERFERON-2a IN THE TREATMENT OF SYSTEMIC SCLEROSIS

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SUMMARY

Systemic sclerosis (SSc) is a multisystem disorder characterized by deposition of excessive amounts of collagen. The interferons are a group of polypeptides which exhibit anti-viral, antiproliferative and immunomodulator effects. It was reported that interferon (IFN) alpha inhibited collagen synthesis by human dermal fibroblasts in vitro. In this study, we studied the effects of IFN-a on dermal and pulmonary involvement in patients with SSc. A total of 15 patients with SSc (8 pulmonary involvement), 15 women, aged between 28 and 63 years (mean:50.6 ± 9.35) were studied. Recombinant IFN-a was given subcutaneously $3x10^6$ IU three time a week. Skin score were calculated with the modified Rodnan skin score. The differences between the initial of IFN therapy and twelfth months values were calculated by using the Wilcoxon method. The skin score evaluation; initial skin score 18.33 ± 8.25, after 12 months 6.0 ± 2.72, this fall was statistically significant (P<0.001). Pre and post-treatment lung function tests were not changed. New pulmonary and gastrointestinal involvements were seen only in two patients during the treatment. Fever and headache were seen in 5 patients, fever and permanent neutropenia in 1, fever and permanent liver dysfunction in 6. As a result, in this preliminary study, IFN-a in the dosage we used provides significant improvement in skin manifestations. It did not cause regression of lung lesions and did not prevent new lung lesions and other organ involvements.

Key words: *Systemic sclerosis, Interferon alpha*

ÖZET

Sistemik skleroz tedavisinde alfa interferon 2a'nın klinik ve laboratvar etkileri

Sistemik skleroz (SSc) aşırı miktarda kollajen birikimi ile karakterize bir multisistem hastalığıdır. İnterferonlar anti viral, antiproliferatif ve immünomodülatör etkileri olan bir grup polipeptidlerdir. İn vitro olarak interferon alfa'nın insan dermal fibroblastlarının kollajen sentezini inhibe ettiği yayınlanmıştır. Bu çalışmada, biz sistemik sklerozlu hastalarda dermal ve pulmoner tutulum üzerine IFN-a'nın etkilerini çalıştık. Yaşları 28-63 arasında (ortalama: 50.6 ± 9.35) olan toplam 15 kadın sistemik sklerozlu hasta (8 pulmoner tutulumlu) çalışıldı. Rekombinan IFN-alfa haftada 3 kez 10 üzeri 6 IU subkutan olarak verildi. Cilt skoru, modifiye Rodnan cilt skoru ile hesaplandı. Wilcoxon metodu kullanılarak IFN tedavisinin başlangıcı ile 12 aylık tedavi arasındaki farklar hesaplandı. Cilt skor değerlendirilmesi; başlangıç cilt skoru 18,33 ± 8,25, 12 ay sonra 6 ± 2,72, bu düşüş istatistik olarak anlamlı idi (p< 0,001). Tedavi öncesi ve sonrası akciğer fonksiyon testleri değişmedi. Yeni akciğer ve gastrointestinal tutulma, tedavi esnasında yanlızca 2 hastada görüldü. Ateş ve başağrısı 5 hastada, ateş ve sürekli nötropeni 1, ateş ve sebat eden karaciğer fonksiyon bozukluğu 6 hastada görüldü. Sonuç olarak, bu sınırlı çalışmada, bizim kullandığımız dozda IFN-alfa cilt bulgularında belirgin iyileşme sağladı. Bu akciğer lezyonlarında gerilemeye neden olmadı, yeni akciğer lezyonlarında ve diğer organ tutulumlarından korumadı.

Anahtar kelimeler: *Sistemik skleroz, interferon alfa.*

Systemic sclerosis (SSc) is a multisystem disorder characterized by proliferation of vascular tissue, obliterative microvascular lesions and deposition of excessive amounts of normal extracellular matrix components,chiefly collagen (1,2). Systemic sclerosis has two major subsets, diffuse cutaneous SSc and limited cutaneous SSc. Patients with limited cutaneous SSc frequently have an indolent course with mild cutaneous thickening of only the fingers, hands, face and visceral involvement. In contrast, patients with diffuse cutaneous SSc tend to have rapid progression of skin thickening within the first 2-3 years. Patients with extensive

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skin disease have decreased survival and a greater risk of developing scleroderma renal crisis and severe SSc pulmonary interstitial and myocardial disease (3).

The mechanisms which is responsible for the collagen deposition and the microvascular abnormalities are still unknown. Although the pathogenesis of SSc is not completely clear, it is apparent that several products secreted from the types of cells found in mononuclear cell infiltrates can modulate the behavior of fibroblasts (4, 5). Over the past decade, studies from a number of different investigators have demonstrated that the products of inflammatory cells play a role in the regulation of collagen synthesis and degradation in cell culture system (6, 7).

The interferons (alpha, beta, gamma) are a group of polypeptides which exhibit anti-viral, antiproliferative and immunomodulator effects. They have been demonstrated to inhibit collagen synthesis by human dermal and synovial fibroblasts in vitro, especially interferon-g (8, 9). It was reported that interferon-a inhibited collagen synthesis by human dermal fibroblasts in vitro (10, 11). In this study, we studied the effects of IFN-a on dermal and pulmonary involvement in patients with SSc.

MATERIALS AND METHODS

We studied 15 patients with diffuse SSc, 15 women between ages of 28 and 63 years (mean:50.6 ± 9.35). The mean disease duration was 6.26 ± 2.55 years. They were diagnosed according to classification criteria of the American Rheumatism Association (12). No patients were permitted to take antifibrotic, corticosteroid and cytotoxic therapy in the 3 months prior to entering the study. Vasodilatators, antireflux agents (for example sisarid, methoclopramide) and nonsteroidal anti-inflammatory drugs (NSAIDs) were allowed. No patients were entered into this study who were younger than 20 or older than 65 years of age. Patients with hepatobilier and bone marrow dysfunction were not included in this study.

Recombinant interferon alpha (Roferon A, Roche) was given subcutaneously $3x10^6$ units three time a week, for 12 months. Five of the patients who entered the study had not previously received any anti-fibrotic therapy. Ten had been treated with D-penicillamine until three months ago.

The patients were examined monthly intervals by same doctor until completion of the study. Skin score were calculated with the modified Rodnan (13) skin score (0= normal skin thickness, 1= mild skin thickness, 2= moderate skin thickness and 3= severe skin thickness). Total score was calculated for each of 17 surface anatomic areas of the body; face, anterior chest, abdomen, the fingers, dorsum of hands, forearms, upper arms, thighs, lower legs and dorsum of feet (total 0-51).

At each examination, routine urinalysis, full blood count, creatinine, urea, hepatic enzymes, lung function tests, chest x-ray, high resolution pulmonary computerized tomography, cine eosephagogram or fluoroscopy, electrocardiogram, echocardiogram, rheumatoid factor, antinuclear antibody, complement levels were determinated. All clinic features of the patients before IFN-a treatment were shown at Table 1.

The differences between the initial and 12 months values were calculated using the Wilcoxon method.

Table 1. Clinical features of the patients with SSc before IFN treatment

	Patients (n=15)	%
Skin involvement	15100	
Raynaud's phenomenon	15	100
Pulmonary involvement	8	53
Esophageal involvement	6	40
Secondary Sjögren's syndrome	6	40
Arthralgia	10	66
Contracture	6	40
Pericarditis	5	33
Myalgia	4	26
Calcinosis	3	20

RESULTS

We evaluated 15 patients every month. The skin score evaluation; initial skin score 18.33 ± 8.25, after 3 months 14.2 ± 4.82, after six months 12.4 ± 3.55, after 9 months 10.3 ± 3.28, after 12 months 6.0 ± 2.72. This reduction was statistically significant ($P<0.001$).

Pre and post-treatment median CO diffusion capasity (85.06±19.37 and 84.57±23.03 ml/min/mmHg respectively) was not changed. New pulmonary and gastrointestinal involvements were seen only in two patients during the treatment. Deterioration in CO diffusion test was seen in three patients, although it was remained unchanged in others. There was no statistically significant variation before and after therapy in the mean CO diffusion test. In

the beginning of the study, gastrointestinal tract involvement and arthralgia were determined in 6 patients, after 12 months there were 8 patients. Evaluation of pre and post-treatment datas are shown Table 2, 3 and 4. There were no changes in immunological parameters, such as ANA, IgG, IgA, IgM, C3 and C4 components. Raynaud's phenomenon, secondary Sjögren's syndrome, contractures of hands, pericarditis, renal involvement and calcinosis did not change during the therapy.

Fever and headache were seen in 5 patients, fever and permanent neutropenia in 1, fever and permanent liver dysfunction in 6.

DISCUSSION

Systemic sclerosis is an uncurable disease. Today, the type of the disease, organ involvement, early diagnosis, to determine the risk groups and well understanding of pathogenesis is very important for prognosis. It is very important to choose the most appropriate treatment according to vascular, immunological data and fibrosis. The effects of modified drugs on survive is unclear, although supporting therapies provides partial improvement (14).

Table 2. Comparison of pre and posttreatment clinical manifestations

Features	Before treatment	After treatment	P
Skin score	18.33 ± 8.25	6.0 ± 2.72	P<0.001
Raynaud phenomenon	15	15	P>0.05
Pulmonary involvement	8	10	P>0.05
Esophageal involvement	6	8	P>0.05
Secondary Sjögren's syndrome	6	6	P>0.05
Arthralgia	10	8	P>0.05
Contracture	6	6	P>0.05
Pericarditis	5	5	P>0.05
Myalgia	4	4	P>0.05
Calcinosis	3	3	P>0.05

Although suppression of T cell activation and decreasing production of cytokines change the outcome of SSc, the effects of conventional immunosuppressive therapies have not proved (15). Also we don't have enough knowledge about drug combinations. Anti-fibrotic drugs (colchisin and D-penicillamine) decreases collagen synthesis but they are not successful complete remission in treatment (16, 17). Penicillamine does not have the same effect in every form of SSc (18, 19).

The roles of T cells in pathogenesis of SSc is still unclear. In early sclerodermic lesions T cells are found in great amounts (20). T lymphocytes increase collagen synthesis of fibroblast so anti-thymocyt globulins are used in treatment but the results are variable (3, 21). The mitogenic activity of serum and fibroblasts in SSc patients are decreased by human recombinant IFN-g so that it can be used as a rational treatment (22), but its effect on organ involvement is still unclear. Depending on inhibitory effects of the drug on skin fibroblast, a study was performed and it was shown that skin manifestations were improved (23).

In our study, we investigated the effect of IFN-a on patients who had skin and lung involvement and skin involvement might show dramatic changes in a short time period. Similar study was performed with higher dosage of IFN-a and only skin manifestations were regressed (24). In an another randomized double-blind, placebo-controlled study, it was reported that IFN-a had no value in the treatment of scleroderma (25). In our study, there was significant regression in skin lesions but there was no improvement in lung and organ involvement. We used subcutaneously IFN-α in low dosage. We followed the patients for 12 months. In this period CO diffusion test was decreased in three patients, but only in 2 patients, we determined new lung involvements. Also in 2 patients we determined gastrointestinal involvement. In 8 patients skin scores did not change between 6-12 months of the study. In 2 patients skin scores were increased.

Table 3. Comparison of pre- and posttreatment laboratory parameters

Parametre	Before treatment	After treatment	P
Hb (g/lt)	10.2±2.5	10.8±1.9	P>0.05
Leucocyte	7200 ±2300	6800 ± 3300	P>0.05
Thrombocyte	188000 ± 24000	202000 ± 15000	P>0.05
C3 (g/dl)	0.78±0.35	0.96±0.25	P>0.05
C4 (g/dl)	0.28±0.16	0.25±0.22	P>0.05
CO diffusion test (ml/min/mmHg)	85.06±19.37	84.57±23.03	P>0.05

Table 4. Evaluation of pre and posttreatment high resolution pulmonary CT

	High resolutionpulmonary CT	
	Pretreatment	Posttreatment
Interstitial involvement	8	10
Normal data	7	5

During the therapies there was temporary adverse effects, but we did not stop the therapy. In a short time adverse effects got over. So we believe in SSc patients IFN-a can be safely used in the dosage that we used in our study.

We couldn't find the reason why IFN-a has no effect on pulmonary fibroblasts although it effects skin fibroblasts. So that we planned to investigate IFN receptors of skin and pulmonary fibroblasts in SSc patients.

As a result IFN-a in the dosage we used provides significant improvement in skin manifestations. It did not cause regression of lung lesions and did not prevent new lung lesions and other organ involvements.

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LEFT VENTRICULAR SYSTOLIC AND DIASTOLIC FUNCTIONS IN WILSON DISEASE

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SUMMARY

Wilson disease (WD) is a systemic disease involving many organ systems including heart. Congestive heart failure, arrhythmia, sudden death and cardiomyopathy have been reported in patients with WD. However cardiac functions in WD have not been adequately studied. The aim of our study was to assess left ventricular systolic and diastolic functions in patients with WD.

Eighteen patients with WD (6 female and 12 male, mean age: 10.28 years) and eighteen age matched children were studied. Standard two-dimensional, M-mode and Doppler echocardiographic examination was carried out on each subject. WD was diagnosed by pediatric gastroenterology department on the basis of established criteria. No significant difference was found in fractional shortening, ejection fraction, heart rate, cardiac index, left ventricular end-diastolic volume. However compared with the control group, patients with WD has significantly increased A velocity (61.44±11.68 vs. 55.17±5.72, p<0.05). The tendency for E/A to decrease (1.65±0.48 vs. 1.75±0.21) and for isovolumic relaxation time to increase (58.68±13.3 vs. 54.7±12.3) in patients with WD did not show statistical significance. These abnormalities could be due to an impaired relaxation of left ventricle.

In conclusion, patients with WD may have a diastolic dysfunction though asymptomatic and should be monitored closely by echocardiography for left ventricular functions.

Key words: *Wilson disease, left ventricular diastolic functions, echocardiography*

ÖZET

Wilson hastalığında sol ventrikül sistolik ve diyastolik fonksiyonları

Wilson hastalığı multisistemik bir hastalıktır. Konjestif kalp yetmezliği, aritmi, ani ölüm kardiyomiyopati rapor edilmekle birlikte kardiyak fonksiyonlar yeterince araştırılmamıştır. Çalışmamızda; Wilson hastalığında sol ventrikül sistolik ve diyastolik fonksiyonları araştırılmıştır. Bu amaçla, Wilson hastalığı olan 18 (6 Kız, 12 erket, Ortalama yaş 10, 28) ve kontrol olarak 18 sağlıklı çocuk; 2 boyutlu, M-Model ve Doppler ekokardiyografi ile değerlendirildi. Wilson hastalığı tanısı belirlenmiş kriterlere göre gastroenteroloji bölümünde konuldu.

Ejeksiyon fraksiyonu, fraksiyonel kısalma, kalp hızı, kardiyak indeks ve sol ventrikül diyastol sonu volümü açısından her ki igrup arasında fark bulunmadı (p>0,05). Ancak Wilson hastalarında mitral geç akım hızının kontrol grubuna göre artmış olduğu saptandı (61,44 ± 11,68 vs 55,17 ± 5,72, p<0,05). Wilson hatalığında; E/A oranının azalmış (1,65 ± 0,48 bs, 1,75 ± 1,75 ± 0,21), ızovolümük relaksasyon zamanının ise uzamış olduğu (58,68 ± 13,3 vs 54,7 ± 12,3) ancak istatistiksel olarak anlamlı olmadığıbelirlendi (p>0,05). Bu bulguların sol ventrikül relaksasyon bozukluğuna bağlı olabileceği düşünüldü.

Sonuç olarak; Wilson hastalığı olan hastaların asemptomatik dönemde diyastolik fonksiyon bozukluğu olabileceğini, bu nedenle ekokardiyografik olarak değerlendirmeninuygun olacağını düşünmekteyiz.

Anahtar kelimeler: *Wilson Hastalığı Sol Ventrikül Diyastolik Fonksiyonu, Ekokardiyografi*

Wilson disease (Hepatolenticuler degerenation) is a disorder of hepatobiliary copper excretion manifested predominantly by hepatic and neurologic copper toxicosis and inherited in an autosomal recessive pattern. The gene for Wilson disease (WD) has been mapped to chromosome 13, but the function has not yet been determined. The clinical manifestations of WD are varied and often nonspecific and include a range of hepatic, neurologic, ophtalmologic, hematologic, renal and psychiatric findings (1,2,3). Congestive heart failure, cardiac arrhythmias, sudden death and cardiomyopathy have been reported in patients with WD (4,5). However, cardiac functions have not been adequately studied. The aim of our study has been to as-

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sess left ventricular systolic and diastolic functions in patients with WD.

MATERIALS AND METHODS

Eighteen patients (12 male and 6 female) aged 10.28 years (range: 5-15 years) with WD were studied by means of Doppler echocardiography. WD was diagnosed by pediatric gastroenterology department on the basis of established criteria, including the history of the patient and his family, physical examination, liver function tests, serum ceruloplasmin and copper levels, urinary Cu excretions, liver biopsy (when necessary) and hepatic Cu concentrations. Twenty healthy age-matched children were taken as a control group. Informed consent was obtained from each participant before the study. Two-dimensional and M-mode echocardiographic examination were performed to determine left ventricular systolic functions. Images were obtained on a HP Sonos 1000 echocardiogram with 3.5/2.7 MHz and 5.0/7.5 MHz transducer. Recordings were done the subject in supine position and breathing freely. M-mode tracings were obtained at the level of the tips of the mitral leaflets in the parasternal long axis position and measurements were performed according to the American Society of Echocardiography recommendations. We obtained interventricular septal thickness in diastole (IVSd), interventricular septal thickness in systole (IVSs), left ventricular end diastolic dimension (LVEDD), left ventricular end systolic dimension (LVESD), left ventricular posterior wall thickness in systole (LVPWDs), left ventricular posterior wall thickness in diastole (LVPWDd), and R-R interval. Left ventricular end diastolic volume (LVEDV), left ventricular end systolic volume (LVESV), ejection fraction (EF), fractional shortening (FS), stroke volume (SV), and cardiac output (CO) were calculated from these data using Teicholz method digitally and left ventricular mass (LV Mass) were determined using Penn's formula. Pulsed Doppler was used to investigate left ventricular transmitral flow by placing the Doppler cursor line parallel to flow as much as possible and the sample volume between the tips of the mitral valve leaflets. The following variables were analyzed: the early peak of velocity of mitral inflow (Peak E), the late peak of mitral inflow (Peak A), the ratio of early peak to late peak filling velocities (E/A ratio), the deceleration time of peak E velocity (DT), and the acceleration time of mitral inflow to peak E (AT). Doppler signals were analyzed from three cardiac cycles to calculate a mean value for each variable. Isovolumic relaxation time (IRT) was measured with the probe at apical 5-chamber position while the sample volume was placed between the aorta and the mitral valve, where the recordings of both valves were taken simultaneously.

STATISTICAL ANALYSIS

Data were expressed as mean ± standard deviation. Statistical analysis was performed by using the student's t test. Significance was established at $p < 0.05$.

RESULTS

The clinical details of our patients are shown in Table 1. Ascites was absent or slight in 15 patients and dense in 3 patients. The follow-up duration of our patients was 26 months (range: 8-31 months). All of the patients had hepatic involvement, 2 patients had hepatic and neurologic involvement, 3 patients had renal manifestations and 4 patients had hematologic manifestations. Liver biopsy was performed in 14 patients, 6 of them had cirrhosis, 5 of them had chronic active hepatitis and 3 had hepatic steatosis.

No significant difference was found in heart rate, left ventricular end diastolic volume, stroke volume, fractional shortening, cardiac index, and other left ventricular systolic indexes between the groups. Ejection fraction and fractional shortening stayed within normal range. No difference was found in left ventricular mass between the groups (64.99±22.1 vs. 66.68±16.3). Heart rate was similar in both groups. Left ventricular systolic parameters of WD and control group are shown in Table 2.

Compared with the control group, patients with WD had significantly increased peak A velocity (61.44±11.68 vs 55.17±5.72, $p<0.05$). There was a tendency for E/A to decrease (1.65±0.48 vs

Table 1. Clinical and some laboratory findings of patients with WD

Age	5-15 years (mean:10.3 years)
Male/female ratio	2:1
Follow-up duration	8-31 months (mean:26 months)
Hepatic form	16 patients (88.8 %)
Hepatic+neurologic form	2 patients (11.1%)
Tubuler dysfunction	3 patients (16.6 %)
Thrombocytopenia	4 patients (22.2%)
Ascites	3 patients (16.6 %)
Ceruloplasmin <20µg/dl	14 patients (78 %)
Serum Cu < 75µg/dl	9 patients (52 %)
Urine Cu >100 µg/dl	15 patients (82%)

Table 2. Systolic parameters of groups

	WD	Control	p
LVEDD(mm)	40.8±5.9	39.72±4.2	NS
LVESD(mm)	26.15±4.2	24.85±2.95	NS
IVSd(mm)	9.03±1.4	8.98±1.1	NS
LVPWd(mm)	5.86±1.0	6.33±1.3	NS
LV Mass(gr)	64.99±22.1	66.68±16.3	NS
LVEDV(ml)	75.77±27.7	71.81±19.2	NS
LVESV(ml)	26.15±11.4	22.52±6.8	NS
SV(ml)	49.74±18.0	49.27±18.9	NS
CI(lt/min/m^2)	3.81±1.1	3.65±1.0	NS
Heart rate	91±11.3	84.11±10.9	NS
EF(%)	65.66±4.6	65.94±10.1	NS
FS(%)	35.44±3.6	37.5±4.3	NS
WS(gr/cm^2)	71.37±23.6	68.05±15.3	NS

LVEDD: Left ventricular end diastolic diameter
LVESD: Left ventricular end systolic diameter
IVSd: Interventricular septum diastolic thickness
LVPWd: Left ventricular posterior wall diastolic
LV Mass: Left ventricular mass
LVEDV: Left ventricular end-diastolic volume
LVESD: Left ventricular end-systolic volume
SV: Stroke volume
CI: Cardiac index
EF: Ejection fraction
FS: Fractional shortening
WS: Wall stress

1.75±0.21) and for IRT to increase (58.68 ± 13.3 vs. 54.7 ± 12.3) in patients which did not show statistical significance. These abnormalities could be due to an impaired relaxation of left ventricle. Left ventricular diastolic parameters are shown in Table 3.

DISCUSSION

WD is a disorder of hepatobiliary copper excretion manifested predominantly by hepatic and neurologic copper toxicosis. The clinical sequela of WD result from excessive deposition of Cu in various body tissues (1). Cardiac manifestations in WD include arrhythmias, cardiomyopathy, sudden death and autonomic dysfunction as reported by Kuan et al (4). They evaluated 53 patients and found ECG abnormalities in 34 % (left ventricular hypertrophy, ST-T changes, premature atrial contractions, premature ventricular contractions and atrial fibrillation) and orthostatic hypotension in 19 % of patients. Two patients had died due to ventricular fibrillation and dilated cardiomyopathy respectively (4).

Table 3. Diastolic parameters of groups

	WD	Control	p
Peak A(cm/sec)	61.44±11.6	55.17±5.7	<0.05
Peak E(cm/sec)	98.0±14.6	96.5±11.3	NS
E/A	1.65±0.4	1.75±0.2	NS
IRT(msec)	58.68±13.3	54.7±12.3	NS
AT/msec)'	76.38±18.5	74.47±15.8	NS
DT(msec)	136.5±36.9	121.1±28.8	NS

IRT: Isovolumic relaxation time
AT: Acceleration time
DT: Deceleration time

In our study Doppler echocardiography showed an impaired left ventricular diastolic filling characterized by increased late diastolic flow velocity. The tendency for E/A ratio to decrease and for IRT to increase in patients with WD did not reach statistical significance. These abnormalities could theoretically be due to a decrease in preload, to an increase in afterload, or to an impaired relaxation of left ventricle (6). It is unlikely that our results depend on a decrease in preload. A decrease in preload may induce a decrease in E velocity and E/A ratio. In our patients we observed decreased E/A ratio, but peak A was increased and peak E was similar to those of controls. Furthermore, the increase in LVEDV in our patients (75.77±27.78 vs. 71.8±19.21) suggest an increase in preload. An increase in afterload could be excluded in our patients because of reduction in peripheral resistance. Wall stress calculated by echocardiography is a good indicator of afterload (6,7). In our study the wall stress values in both groups were similar indicating that the changes were not due to increase in afterload in patients with WD. We think that these abnormalities result from impaired relaxation of left ventricle.

The mechanisms for the abnormalities in diastolic filling in WD have not been established. Relaxation abnormalities are one of the earliest signs of cardiac dysfunction in many disease states. This pattern is similar to the Doppler variables reported in systemic hypertension, hypertrophic cardiomyopathy, and cardiac amiloidosis (8). The major pathological findings of the myocardium in WD include interstitial myocardial fibrosis, intramyocardial small vessel disease, focal myocarditis and cardiac hypertrophy. Copper concentrations were increased in 5 of 9 hearts in which spectrophotometric analysis was carried out, but histochemical staining failed to show where the copper was localized (5). A recent report by Kaduk et al. describing cardiomyopathy in WD suggested that mitochondrial alterations were the consequence of the accumulation of myocardial copper (9). Azevedo et al. reported that copper concentration on a myocardial biopsy fragment was almost 10 times the normal heart content (10). We can speculate that, in early stages of WD, there may be a lesser accumulation of the myocardium but that it is sufficient to alter the relaxation process. As the disease prolongs, changes leading to cardiomyopathy also occur. Therefore it is important to follow and monitorize patients with WD by echocardiography.

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THROMBOCYTOPENIA IN THE NEONATE*

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SUMMARY

Thrombocytopenia, a platelet count of less than 150.000 per m.liter occurs relatively frequently in sick and well newborns. In some cases, it is mild and does not require any therapy. However, severe thrombocytopenia can lead to a life threatening hemorrhage and making the correct diagnosis is important for providing the appropriate treatment.

We performed a one year retrospective study of 300 infants admitted to Neonatal Intensive Care Unit of Ankara University to determine the frequency, cause, treatment and prognosis of thrombocytopenia. Clinically significant thrombocytopenia developed in 12 (4%) of the infants admitted to the intensive care unit. Mean birth weights of these 12 patients was 2342 ± 962 g, mean gestational age was 36.3 ± 3.9, mean platelet count was 51.083 ±. 19.157 mm^3. Among 3 otherwise healthy thrombocytopenic infants, one had low maternal platelet count and the baby was diagnosed as autoimmune thrombocytopenia secondary to maternal Immunthrombocytopenia (ITP) and treated with Intravenous Immune Globulin (IVIG) and steroid. Other two were diagnosed as alloimmune thrombocytopenia treated with IVIG. In all cases potential cause for thrombocytopenia could be found. Out of 12 patients, 9 recovered completely, 2 were died of sepsis and 1 is still in the follow up.

In this article neonatal thrombocytopenia is briefly discussed and an algorithm for the diagnosis were given.

Key words: *Thrombocytopenia, Newborn*

ÖZET

Yenidoğanda Trombositopeni

Sağlıklı ve hasta yenidoğanda göreceli olarak sıklıkla oluşan trombositopeni, trombosit sayımının 150x109/L'nin altında bulunması olarak tanımlanır. Tedavi gerektirmeyen hafif trombositopenilerin dışında yaşamı tehdit eden kanamalara neden olan ciddi trombositopenilerde doğru tanı ile uygun tedavi verilmesi önemlidir.

Yenidoğanda trombositopeni sıklığı, nedenleri, tedavi ve prognozu belirlemek amacı ile Ankara Üniversitesi Yenidoğan Yoğunbakım Ünitesinde son bir yılda yatarak izlenen 300 hastanın dosyaları retrospektif olarak incelendi. Yenidoğan Yoğunbakım Ünitesine başvuran 12(%4) hastada klinik olarak belirgin trombositopeni saptandı. Bu olguların ortalama doğum ağırlıkları 2342±962 g., ortalama gestasyon yaşları 36.3±3.9 hafta, ortalama trombosit sayımları 51.03±19.15x109/L bulundu. Üç sağlıklı ancak trombositopenisi olan yenidoğandan bir olgu, annede immuntrombositopeni olması nedeniyle otoimmun trombositopeni tanısı alarak intravenöz immunglobulin (İVİG) ve steroid ile tedavi edildi. Diğer 2 olguda ise alloimmün trombositopeni tanısı konarak İVİG tedavisi uygulandı. Bütün olgularda trombositopeniye neden olan hastalıklar saptandı. İncelenen 12 hastadan 9'u tamamen iyileşti, 2 olgu sepsis nedeniyle kaybedildi, 1 olgunun ise izlemi devametmektedir.

Anahtar kelimeler: *Trombositopeni, Yenidoğan.*

A platelet count of less than 150x10^9/L is abnormal in term and premature infants. Clinically significant thrombocytopenia defined as a platelet count of less than 50x10^9/L is an important problem in the newborn period, particularly in sick premature neonates (1).

Mild asymptomatic thrombocytopenia is relatively common in healthy term newborns being present in cord blood sample in 4% of 2200 pregnancies ; however clinically significant thrombocytopenia is uncommon and observed only in 0.12% of more than 15000 newborns (2-4).

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The level of platelets in the blood reflects a balance between their production and destruction .Thrombocytopenia may result from decreased production, increased destruction and a combination of both (5,6). Decreased number of platelets with bonemarrow megakaryocytic hyperplasia and the presence of megathrombocytes in a peripheral blood smear are characteristics of thrombocytopenia due to increased peripheral destruction of platelets (1,2). Many other factors contribute to thrombocytopenia . Thrombocytopenia infants are significantly more likely to have higher hemoglobin values, lower 5 minute APGAR scores, be on antibiotics and have central or peripheral venous catheters in place than sick but non thrombocytopenic infants (1,2,6-8).The most common causes of thrombocytopenia appear in Table I.

MATERİAL AND METHOD

A retrospective analysis of all the thrombocytopenic newborns admitted to the intensive care unit in Ankara University Hospital from November 1996 to November 1997 was done. Neonatal Intensive Care of Ankara University is a reference third level of care center which admits both inborn and outborn patients. Number of admissions per year is about 300-350 each year.50% of the patients are inborn while the other 50% are referred from other regional maternity hospitals. All of the admissions are registered and patient files are kept in the department archives.

Complete blood counts of the patients are conducted in the hematology laboratory of the department via flowcytometric method(Coulter counter T890)Coagulation screening tests are done in the same laboratory using Organon Technica Coagulameter method.

Thrombocytopenia less than 100.000 per ml. Was accepted as clinically significant thrombocytopenia and patients with thrombocyte counts less than 100.000 per ml. were taken as the study group. Hospital records of these patients were reviewed retrospectively. Twelve clinically significant thrombocytopenic cases were identified and the incidence of clinically significant thrombocytopenia was found to be 4 %(12/300).Mean gestational age, birth weight, platelet count were 36.3 ± 3.9, 2342 ± 962 g , 51.083 ±. 19.157 mm^3 respectively. In these patients etiologic factors are demonstrated in Table 2. Clinical characteristics of 12 patients are given in Table 3 and 4.

The first patient is diagnosed as congenital CMV infection . She was born to a renal transplanted mother who had been on immunesupressive therapy. In this patient physical signs such as being small for gestational age, microcephaly and hepatosplenomegaly suggested congenital infection. CMV serology was positive, intracranial calcifications were found in brain tomography. She was only given plasma transfusion and her platelet count increased spontaneously.

Table 1. Causes of neonatal thrombocytopenia

- DECREASED PRODUCTION OF PLATELETS
  - * Congenital megakaryocytic hypoplasia
    - Thrombocytopenia absent radius syndrome
    - Megakaryocytic hypoplasia without anomaly
    - * Congenital leukemia and histiocytoses
    - * Inherited thrombocytopenia
    - Wiscott Aldrich syndrome
    - Other X-linked or recessively transmitted thrombocytopenia
- INCREASED DESTRUCTION OF PLATELETS
  - * Immune thrombocytopenia
    - Neonatal alloimmune thrombocytopenia
    - Neonatal autoimmune thrombocytopenia
    - Drug induced thrombocytopenia
  - * Giant hemangioma syndrome
  - * Other states with DIC
- BOTH DECREASED PRODUCTION AND INCREASED DESTRUCTION
  - * Infections
    - Congenital usually viral
    - Acquired usually bacterial
  - * Osteopetrosis

Table 2. Causes of thrombocytopenia

Etiologic factors	n (%)
Sepsis and DIC	3 (%25)
Immune thrombocytopenia	3 (%25)
Asphyxia and DIC	2 (%16)
Maternal preeclampsia	2 (%16)
Congenital CMV infection	1 (%8)
Bernard Soulier Disease	1 (%8)

Table 3. Characteristics of the infants

Birth weights (g) (x ±2SD)	2342 ± 962
Gestational age (wk) (x ±2SD)	36,3 ± 3,9
Platelet counts (X 10^9 /L) (x ±2SD)	51 ± 19
Positive blood culture (%)	%25
Low maternal platelet count (%)	%8
Birth asphyxia (APGAR 5'< 7) (%)	%50
Mortality (%)	%16

Table 4. Clinical characteristics of patients

Case	Gestational age week	Birth weight gr.	APGAR 5′	Maternal thrombocyte number	Thrombocyte number X10^9/L	Diagnosis	Treatment	Prognosis
1	37	1500	5	Normal	63	Congenital CMV infection	plasma transfusion	Recovery
2	39	3020	7	Normal	33	Bernard Soulier	-	Follow up
3	28	1390	5	Normal	30	Sepsis and DIC	plasma and thrombocyte transfusion	Recovery
4	40	3200	7	Normal	31	Sepsis and DIC	plasma and thrombocyte transfusion	Exitus
5	34	1300	6	Normal	32	Sepsis and DIC	plasma and thrombocyte transfusion	Exitus
6	38	2400	7	Normal	66	Maternal preeclampsia, DIC, Down syndrome	plasma and thrombocyte transfusion	Recovery
7	33	1320	3	Normal	67	Maternal preeclampsia	plasma and thrombocyte transfusion, heparinization	Recovery
8	40	4200	8	Normal	61	Alloimmune thrombocytopenia	IVIG	Recovery
9	40	3200	8	Normal	35	Alloimmune thrombocytopenia	IVIG	Recovery
10	40	3000	9	Low 60.000/ mm^3	40	Autoimmune thrombocytopenia	IVIG, steroid	Recovery
11	35	1900	3	Normal	79	Asphyxia and DIC	plasma transfusion	Recovery
12	32	1680	6	Normal	76	Asphyxia and DIC	plasma transfusion	Recovery

The second patients who was diagnosed as Bernard Soulier disease had low platelet count and giant platelets and a functional platelet defect in addition to positive family history. He has still low platelet count.

The next 3 patients were diagnosed as culture positive sepsis . In addition to hematologic parameters of sepsis blood studies revealed prolongation of screening tests (prothrombin time, partial thromboplastin time) elevated fibrin degradation products and hypofibrinogenemia. Subsequently DIC developed. They were treated with antibiotics, plasma and thrombocyte transfusions. Unfortunately two of them died of septic shock. One recovered in the 2nd week of treatment.

Two patients had maternal preeclampsia resulting in intrauterine hypoxia and suppression of the megakaryocytic series of the bone marrow for the favor of erythroid hyper plasia. They developed DIC and were treated with plasma, thrombocyte transfusions and heparin.

The infants who were diagnosed as alloimmune thrombocytopenia were term and otherwise healthy babies. Cutaneous bruising and petechia were the only abnormalities found in physical examination, they had isolated thrombocytopenia with normal maternal platelet counts and in these patients no other specific cause of thrombocytopenia can be identified. They were treated with intravenous immunoglobulin (IVIG) dose of 1 g/kg/day for two consecutive days and recovered subsequently. The neonate who had a mother with ITP, was diagnosed as autoimmune thrombocytopenia and recovered with IVIG and steroid (prednisolone) dose of 2 mg/kg/day for two weeks. In the other 2 patients hypoxia due to abruptio placenta was found to be the only cause of thrombocytopenia, they were treated with plasma transfusions.

DISCUSSION

The approach to thrombocytopenic infants varies according to whether the infant seems well or sick(Figure I) Because the majority of thrombocytopenic cases are secondary to other disease processes, a careful birth history must include associated disease such as hypoxia, infection, maternal illness. One of our patients had the history of maternal renal transplantation

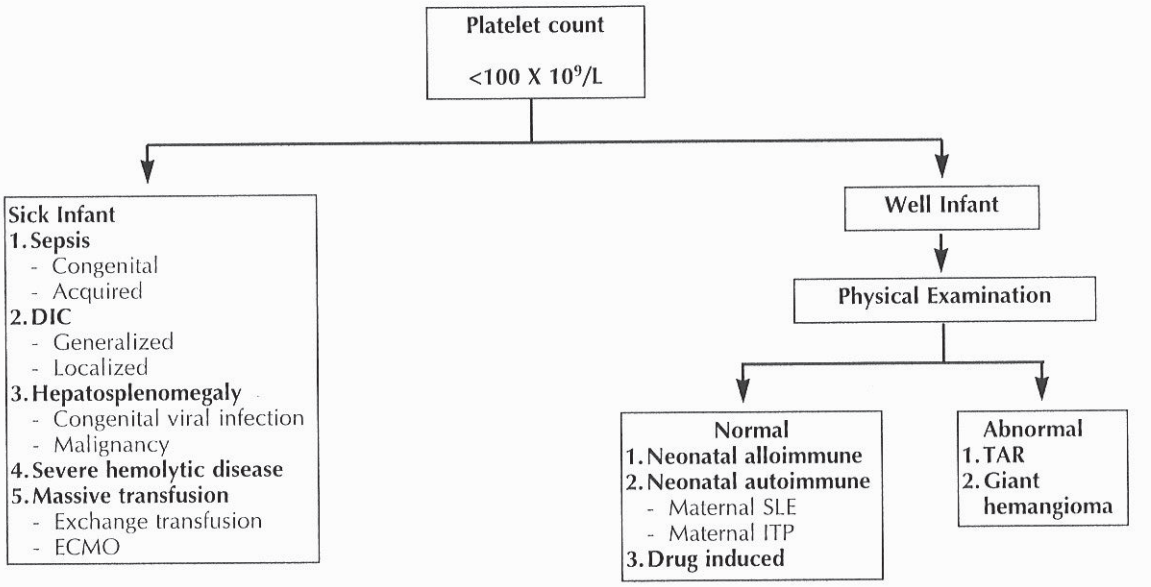

Figure 1. An algorithm for the diagnosis of neonatal thrombocytopenia

and immunesupressive therapy. The baby was diagnosed as congenital CMV infection. In addition, a family history should be obtained with particular attention to maternal thrombocytopenia, maternal medication, and thrombocytopenia in previous siblings and relatives (2). In one of our patients, family history revealed thrombocytopenia in the other family members. He was subsequently diagnosed as Bernard Soulier disease, while other patient had low maternal platelet count and was subsequently diagnosed as autoimmune thrombocytopenia. The physical examination should include particular attention to the skeletal structure of the extremities in order to rule out TAR syndrome (1). Physical signs such as being small for gestational age, microcephaly or hepatosplenomegaly usually suggest a congenital infection as in the case of our patient with congenital CMV infection. Finally a careful examination with auscultation must be made for the presence of an occult hemangioma associated with low platelet count as can be seen in Kassabach Merrit syndrome.

The laboratory investigation begins with complete blood count including mean platelet volume and an examination of the peripheral blood smear for giant platelets or leukocyte inclusions. Presence of very small platelets is consistent with the diagnosis of Wiskott Aldrich syndrome. If the patient is ill or has hemorragic manifestation in excess, other coagulation testing should be performed to investigate for DIC (5). A platelet count also should be performed on the mother. In the case with autoimmune thrombocytopenia maternal thrombocytopenia in the otherwise healthy neonate brought the diagnosis. (Figure 2) Without an obvious cause, if thrombocytopenia is severe maternal, paternal and fetal platelet antigen type and specific circulatory antiplatelet antibodies can be identified. For thrombocytopenic neonates for whom the cause is not clear, bone marrow examination is necessary. In none of the alloimmune thrombocytopenia cases platelet antigen typing could be performed. In cases of alloimmune thrombocytopenia the mothers were negative and the fathers were positive for the platelet specific antigen (9,10).

In the treatment of neonatal thrombocytopenia the most important step is the identification and the control of the underlying disorder as the majority of cases with thrombocytopenia are secondary to other disease processes. It is recommended that treatment must aim to maintain a platelet count more than 50.000 per ml. Current treatment for thrombocytopenia resulting from primary production defect is repeated platelet transfusion. In the neonatal thrombocytopenia secondary to disease processes such as infection and hypoxia treating the underlying cause is crucial in addition to the use of platelet transfusion to decrease the risk of seri-

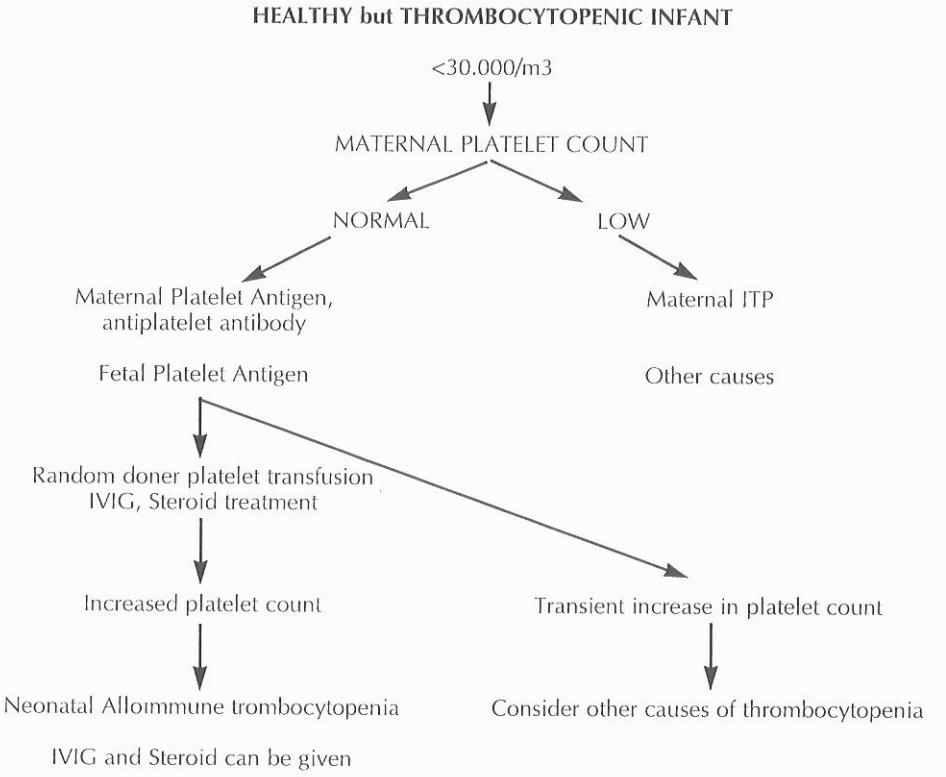

Figure 2. An algorithm for the diagnosis of Alloimmune thrombocytopenia

ous hemorrhage (6,9,10). In the management of maternal autoimmune thrombocytopenia, the treatment is aimed to prevention of intracranial hemorrhage during vaginal delivery (3,4). If the antibody is present in the maternal plasma or if fetal scalp platelet count is less than 75.000 per ml. there is an increased risk of intracranial hemorrhage (3,4). Administration of corticosteroids, IVIG or exchange transfusion will be beneficial. The principle of the management in isoimmune thrombcytopenia is transfusion platelets lacking the incompatible antigen. These are usually obtained from the mother. IVIG to the patient and to the mother in subsequent pregnancies is necessary since the risk of recurrence in subsequent pregnancies is 75% (2).

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ANNULAR PANCREAS AND ITS ASSOCIATION OF MORTAL ANOMALIES

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SUMMARY

One of the most important and urgent problem of the neonate is congenital duodenal obstruction. Annular pancreas is an extrinsic factor that leads to duodenal obstruction. A retrospective review of surgical newborns with intestinal obstruction was performed. The incidence of annular pancreas and its association with other highly mortal congenital anomalies, methods of diagnosis and treatment were discussed.

Key words: *Annular pancreas, neonate*

ÖZET

Anüler Pankreas ve Birlikte Görülen Ölümcül Yandaş Anomaliler

Yenidoğandaki en önemli acil sorunlardan biri doğumsal duodenum tıkanıklığıdır. Anüler pankreas duodenal tıkanıklığa yol açan dışsal nedendir. Barsak tıkanıklığı nedeniyle ameliyat edilen yenidoğanlar gözden geçirilmiştir. Anüler pankreas ve birlikte görülen ölümcül yandaş anomalilerin sıklığı, tanı ve sağaltım yöntemleri tartışılmıştır.

Anahtar kelimeler: *Barsak tıkanıklığı, anüler pankreas, yandaş anomaliler*

One of the most important and urgent problem of the neonate is congenital duodenal obstructions. These obstructions may be intrinsic or extrinsic. On the sixth week of fetal life, the rapidly growing epithelium obliterates the lumen of the duodenum and becomes recanalized at the 12th week. The standstill of this growth or insufficient recanalization give rise to atresia, stenosis or web formation. The leading formation that obstructs the duodenum extrinsically is annular pancreas (AP). The second most is Ladd bands due to malrotation (1). Annular pancreas which has a major associated anomaly rate is one of the surgical procedures that has to be corrected immediately in the neonate. Delay of diagnosis and high incidence of associated anomalies may lead to increase of morbidity and mortality.

MATERIALS ANDMETHODS

The 82 surgical neonates with intestinal obstructions that were operated between 1989 and 1998 were retrospectively evaluated according to the level of gastrointestinal obstruction and associated anomalies.

RESULTS

Eighty-two neonates were referred due to intestinal atresia and other bowel obstructions. Five of these patients were diagnosed as annular pancreas (AP) (Table-1). Male: female ratio in AP was 3:2. Only one of these patients was diagnosed prenatally, the other four presented with bilious vomitting, distension of the upper abdomen, and double bubble sign on plain erect neonatogram. (Table 1)

Two of these AP cases showed tiny air particles in the proximal jejenum despite double bubble in plain x-rays. Down syndrome in three, malrotation in two, esophageal atresia and tracheoesophageal fistula in one, and endocardial cushion defect, mitral and aortic valve insufficiency in one were the associated anomalies (Table 2). According to this table associated ano-

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Table 1. Surgical newborns with intestinal obstructions

Duodenal obstructions	17
Atresia-stenosis	12
Annular pancreas	5
Jejunoileal obstructions	21
Apple-peel syndrome	6
Simple atresia	15
Colonic atresia	2
Malrotation	8
Overall	**82**

malies related to be higher in AP group than other gastrointestinal obstructions. The choice of surgical procedure in three patiens was duodenoduodenostomy whereas antecolic duodenojejunostomy was the procedure of choice in two. The suture material for the formation of anastomosis was 5/0 polyglactin. Two of the patiens failed to thrive due to the associated mortal anomalies. Other three were discharged uneventfully.

DİSCUSSİON

Annular pancreas usually obstruct the duodenum extrinsically and cause duodenal atresia. Rarely there is so tight stenosis that tiny air particles can pass distally. Pancreas occurs ventrally and dorsally as an endodermal bud from the foregut of the embryo on the fourth week of gestation. Ventral part conjoin the dorsal part after growing to the right and posterior of the duodenum. If ventral part of the pancreas stay attached to the duodenum, it forms an annular ring that surrounds the duodenum and causes variable degree of stenosis. (2,3,4)

Table 2. Associated anomalies in intestinal obstructions

Annular Pancreas	
Down's syndrome	3
Malrotation	2
Cardiac defects	1
EA+TEF	1
Overall	*7*
Duodenal atresia and stenosis	
Malrotation	1
Down Syndrome	2
EA+TEF	2
EA	1
Meckel diverticulum	1
Anal atresia	3
Polydactyly	1
Overall	*11*
Jejunoileal atresia	
Malrotation	1
Colonic atresia	1
Volvulus of the sigmoid colon	1
Meckel's diverticulum	1
Distal femoral agenesis	1
Pes equinovarus	1
Metacarpophalangeal deviations	1
Overall	*7*
Total	**25**

Two types of AP was defined as extramural and intramural. Extramural type causes upper gastrointestinal obstructions. Intramural type AP is not well known but leads to duodenal ulcer formation.

Duodenal obstructions can be diagnosed via prenatal ultrasonography by demonstrating the dilated proximal duedonum. Polyhydroamnios can be seen in half of the mothers of these babies. The possibility of upper gastrointestinal system obstructions in a polyhydroamniotic mother should be always kept in mind (5). The presentation of the symptoms after birth is related with the degree of stenosis and also associated anomalies. The most common presenting sypmtom is vomitting, differ to the site of obstruction; distal or proximal to the ampulla of Vateri either bilious or nonbilious respectively. Some of the babies may present with epigastric distention or peristaltic waves of the stomach that can be seen with naked eye. Demonstration of "double-bubble" sign in a plain x-ray film is diagnostic. Some authors emphasize the benefits of selenium sintigraphy to assure the cause of duodenal obstruction is AP. There is little experience on the demonstration of pancreatic ring with the help of sintigraphy.

In a recent report that was prepared from the data of pediatric surgery and pediatric gastroenterology units of Turkey, a ratio of 54% of hospitalized patients in pediatric surgery wards and 10.3 % of outpatients demonstrated a gastrointestinal malformation. The incidence of AP is 12% among this group (6). In another report by Çakmak et al. It has been demonstrated that19 of 30 duodenal obstructions were diagnosed as AP whereas there were 10 duodenal atresia and 1 duodenal stenosis (7). In our series, among 82 intesitinal obstructions, the incidence of duodenal obstruction was 20.7% (17). Five of these patiens (6%) were AP wheres 11 were duodenal atresia and 1 duodenal stenosis.

One of the most common associated anomalies of duodenal obstructions is Down's Syndrome. The incidence of this association is approximately 30-50 % in

different series. The other associated anomalies with duodenal obstructions are as follows; congenital heart disease, esophageal atresia, imperforated anus, renal anomalies, other trisomy syndromes and some neurologic anomalies (5). The overall incidence of associated anomalies with duodenal obstructions is approximately 45-80%. Kierman et al reported 154 associated anomalies in 140 patients. The most common anomaly in this series was Down's syndrome, and intestinal malrotation, cardiac defects and tracheoesophageal fistula were the following respectively (1,5). The association of other congenital anomalies with AP was not studied in most of the reports. The distribution of 82 intestinal obstruction patients in our series were as follows; 17 (20.7%) duodenal obstruction (five of them AP), 25.6% jejunoileal atresia, 9.7% malrotation, 2.4% colonic atresia. The incidence of associated anomalies was 50% in duodenal atresia and stenosis, and there were 11 associated anomalies. Three of the 5 AP patients had an associated anomaly and the total count of anomalies was 7. The rate of Down's syndrome and duodenal obstruction association was 16.6%. This ratio was 60% in AP. These data are in accordance with the other reports of this subject. But the incidence of associated anomalies in AP is significantly high. Here we have to emphasize these association of congenital anomalies with AP.

In these 5 patients with AP, three had Down's syndrome, two had malrotation, one had cardiac defects and one had esophageal atresia and tracheoesophageal stenosis. Two of these patients were dead due to these highly mortal associated anomalies. The other three was discharged from the hospital uneventfully. Technological advances in current surgical concepts and the efficient use of total parenteral nutrition raise the survival rate from 60% to 95%. The association of esophageal atresia and tracheoesophageal fistula in one of these patients and mitral and aortic valve insufficiency and ventricular septal defect in another could easily explain the reason of mortalities. There is reallya strong correlation among the existence of associated anomalies in a surgical newborn.

Some of the AP patients present with symptoms as old as 30-40 years of age. The most common presenting symptom in these patiens are epigastric pain, pancreatitis, and gastric ulceration. These are often mild and do not relate with other associated anomalies(4). Familial pattern is rare (5,8). ERCP is a useful diagnostic tool in adults and leads to decide surgical strategies in these patients (3,4).

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HYDROMETROCOLPOS IN INFANCY: ANALYSIS OF THREE CASES

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SUMMARY

Three cases of hydrometrocolpos with high vaginal obstruction caused by high vaginal transverse septum leading to gross abdominal distension severe respiratory embarrassment, partial urinary and lower gastrointestinal tract obstruction, high blood pressure and neonatal hemorrhagic disease were successfully managed by an abdominoperineal vaginal pull-through. Hydronephrosis, hydroureters and vaginal dilatation completely disappeared in four-months' follow-up. Cosmetic results were excellent as well. The first two cases now in their postmenarchal period have no problems. The first case had a mixoid liposarcoma on her right shoulder which was completely excised.

Key words: *Hydrometrocolpos, vaginal septum, urogenital sinus, vaginal pull-through, liposarcoma*

ÖZET

Sütçocukluğu çağında hidrometrokolpos: Üç olgunun gözden geçirilmesi

Yüksek vajinal taransvers septumun yol açtığı yüksek vajinal obstrüksiyonlu üç hidrometrokolpos olgusu tartışıldı. Karında belirgin şişlik, solunum sıkıntısı, parsiyel üriner ve alt gastrointestinal trakt obstrüksiyonu, yüksek kan basıncı ve yenidoğan hemorajik hastalığı bulguları ile gelen olgular abdominoperineal vajinal pull-through ameliyatı ile başarılı şekilrde tedavi edildiğler. Olgunların ilk dört aylık izlemlerinde hidronefroz, hidroüreter ve vajinal dilatasyonun tamamen kaybolduğu gözlendi. Kozmetik sonuçlar mükemmeldi. Şimdi ilk iki olgu menarş sonrası dönemde ve sorunları yok. İlk olgunun sağ amozunda bulunan miksoid liposarkom tam olarak çıkarılmıştır.

Anahtar kelimeler: *hidrometrokolpos, vajinal septum, ürogenital sinüs, vajinal pulltrough, liposarkom.*

Obstruction of the vagina and cervical and vaginal excess secretion appears to explain the pathopysiology of hydrometrocolpos (HMC) in infancy.The obstruction may be due to an imperforate hymen which can bulge (5). Persistent cloaca is another cause of vaginal obstruction leading to urine and feaces accumulation in the vagina.This is called urofecocolpos, rather than hydrocolpos (3).

Early and late results of three cases of high vaginal atresia are presented in this paper. All of the cases had been managed in early infancy. The first case had a low grade liposarcoma on her left shoulder when she was twelve years old. This is the first case having a neoplastic disease with hydrometrocolpos due to high vaginal atresia in the current literature.

CASE REPORTS

Case 1: A four-month-old girl was admitted with respiratory distress and an abdominal mass. The infant had vomited bile during the previous 15 days. Voiding urine and stools had been scanty and infrequent since birth, while it was noted that the size of the mass had increased gradually. On admission, the infant was dehydrated, obviously uncomfortable, cyanotic and hypertensive with an average blood pressure of 140/80 mm Hg. A firm mass 25 cm in diameter occupied the entire abdomen and extended fully to the xyphoid process. The infant had an umbilical hernia and polydactyly of both feet (Kaufman-McKusick Syndrome). The karyotype was 46xx. On rectal and perineal examination, a mass situated in front of the rectum was palpated. There were normal labiae with

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upward retraction of the vaginal orifices. There was no hymen and the vagina was represented by a 2 cm deep dimple. Due to female-type hypospadias the external orifice of the urethra could not be visualized. Excretory urogram showed severe bilateral ureteral dilatations, hydronephroses and displacement of the small intestine towards epigastrium. The bladder was displaced by the mass both anteriorly and superiorly and showed a somewhat flattened contrast. Ultrasound of the abdomen revealed a 25 cm diameter cystic mass of which the lower half was filled with debris, situated between the rectum and the bladder. This further caused hydronephroses and hydroureters by compression of the bladder neck and ureters at the pelvic rim (Figures 1, 2).

A laparotomy was performed with a suprapubic transverse skin incision after amelioration of the patient's distress with resuscitative measures. Most of the abdomen was filled with an enormously distended upper vagina. The Fallopian tubes and the ovaries were normal, but the uterus was enlarged, measuring 7x6x4 cm. A foul, cloudy brown, mucoid fluid was aspirated from the vagina after tapping the anterior fornix. The vagina was then incised and emptied of 500 ml of fluid. Anterior vaginal wall was separated from bladder neck with fine dissection. Following this preparation, a U-shaped incision was made in the vestibule and urogenital sinus (UGS) was separated from the rectum as far as the upper vagina. The tunnel thus created was then dilated and the upper vagina was pulled through to the perineum, sutured to the vestibular and labial epithelia and anteriorly to the UGS.

Case 2: A forty-day-old girl, admitted with respiratory distress and abdominal distension since birth. Symptoms apart from the absence of hypertension were similar to that of the previous case. Examination of the perineum under general anesthesia revealed normal labiae with missing hymen and the vagina was represented by a 1.5 cm deep dimple. Excretory urogram

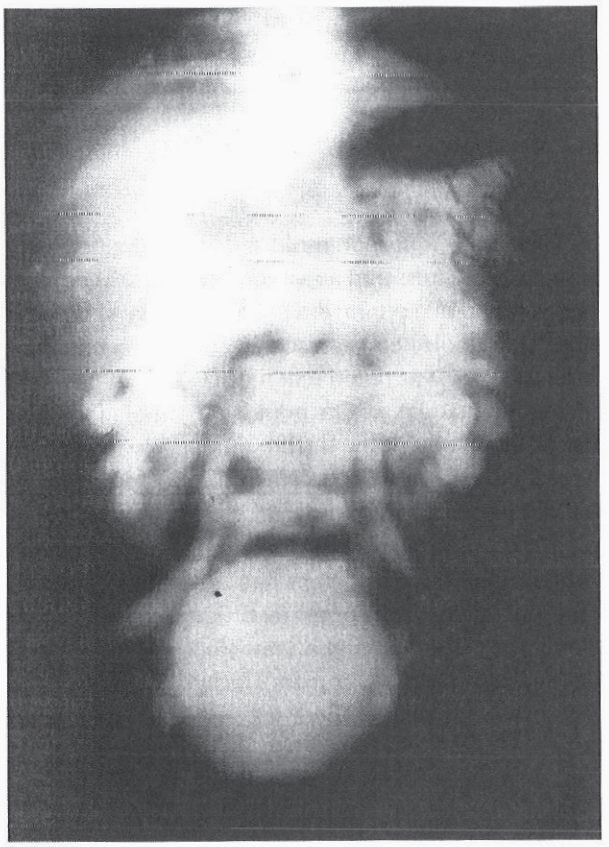

Figure 1. Hydronephroses by compression of the bladder neck in a 4 month old girl

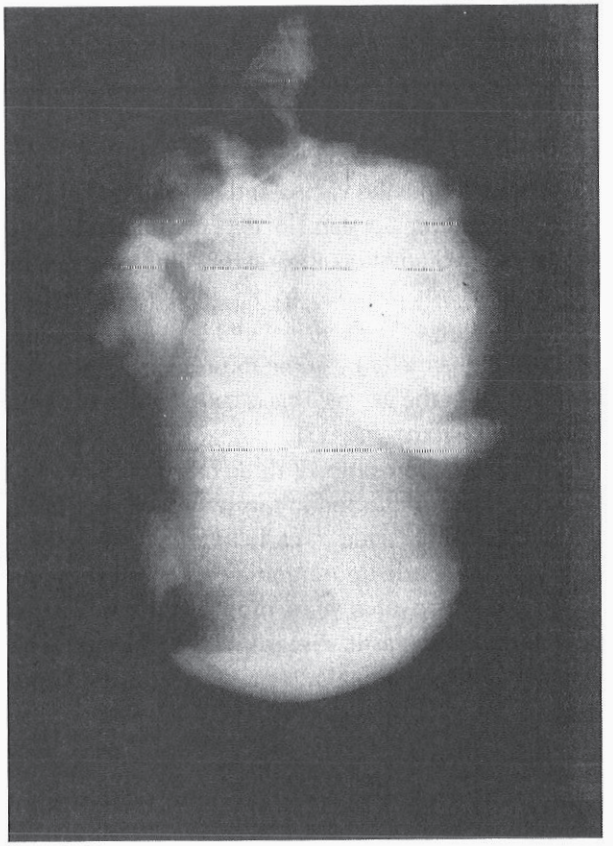

Figure 2. Hydoureteronephroses due to compression of ureters in the pelvic rim in the same patient

showed bilateral hydronephroses and hydroureters and displacement of gut towars the epigastrium by a rounded homogeneous mass. Ultrasound revealed a 20 cm cystic mass situated between the bladder and the rectum, and causing bilateral hydronephroses. The patient's karyotype was 46xx. Laparotomy revealed normal Fallopian tubes and ovaries, but distended upper vagina covering most of the abdomen. The uterus was enlarged, measuring 4x5x3cm. The fluid aspirated from vagina was foul, cloudy-brown and mucoid. The vagina was opened and emptied of 300 ml of fluid. A similar surgical approach in used as the first case and an abdominoperineal vaginal pull-through were carried out.

Case 3: A forty-five-day-old girl, admitted with respiratory distress, projectile vomiting, bleeding per urethra and seizures. History revealed that the newborn had abdominal distention since birth. Cranial CT demonstrated a focal hemorrhage at left parietal lobe. Fibrin, fibrinogen and fibrin degradation products were within normal limits. Physical and laboratory evaluation of the infant indicated a hemorrhagic disease of the newborn presenting with intracranial hemorrhage and urinary bleeding. Hypertension was absent. Examination of the perineum under general anesthesia revealed normal labiae but there was no hymen. The vagina was represented by a 1.5 cm deep dimple. Excretory urogram showed bilateral hydronephroses, hydroureters, and displacement of gut towards the epigastrium by a rounded homogenous mass. Ultrasound revealed a 20 cm cystic mass situated between the bladder and the rectum, causing bilateral hydronephroses. The patient's karyotype was 46XX. The infant was administered 1 mg vitamin K by intramuscular injection for bleeding and phenobarbital 2x10 mg per oral for seizures. A laparotomy performed after the resolution of the intracranial hemorrhage revealed normal Fallopian tubes and ovaries but distended upper vagina covering most of the abdomen.The infant had an uterus didelphys of which both horns were enlarged. The fluid aspirated from vagina was foul, hemorrhagic and mucoid. The vagina was opened and emptied of 300 ml of fluid. The similar surgical approach as used in the first case was employed and thus an abdominoperineal vaginal pull-through was carried out.

In all three cases postoperative vaginal dilatations were performed weekly for a month to prevent stricture formation. Excretory urograms and vaginograms of all cases a month and four months later showed regression of hydronephroses and ureteral dilatations, and decrease in the sizes of the vaginae (Figures 3, 4). Blood pressure of the first case decreased to normal in two months (Table 1). However the first case had developed a five centimeter-diameter mass on her right shoulder. The mass was completely excised and histpathological evaluation revealed a low grade mixoid liposarcoma (Figure 5).

First and second cases had been in postmenarchal period without any problems. The third case is in premenarchal period. All cases had good cosmetic results. The average follow-up period is 10 years.

DISCUSSION

Obstruction of vaginal outlet and secretion of vaginal and cervical glands lead to hydrometrocolps. High vaginal atresiae result from nonfusion of Mullerian ducts and vaginal plate.

The Mullerian ducts develop from the genital ridges and descend caudally and end at the posterior wall of the UGS and form the cord of uterovaginal canal. The sinovaginal bulbs developing in the cranial part of the UGS form the primitive vaginal plate. This obliterates the Mullerian tubercule. The primitive vaginal plate enlarges in all dimensions and invaginates the posterior wall of the UGS causing the sinus to shorten and widen. The urethra is then pulled to its normal anatomical position by the enlargement of the primitive vaginal plate. The vaginal lumen is formed

Table1. Age, symptoms and findings, and karyotype of three infants with hydrometroolpos

Case No	Age	Symptoms and findings	Karyotype
1	4 month old	Abdominal mass Perineal retraction Severe respiratory distress Partial urinary obstruction Partial lower GIT obstruction Hydronephrosis and hydroureters Polydactly of both feet Hypertension, umblical hernia	46XX
2	40 days	Abdominal mass Perineal retraction Respiratory distress Partial urinary obstruction Partial lower GIT obstruction Hydronephrosis and hydroureters Umblical hernia	46XX
3	45 days	Abdominal mass Perineal retraction Respiratory distress Vomiting Hematuria Seizures Hydronephrosis and hydroureter	46XX

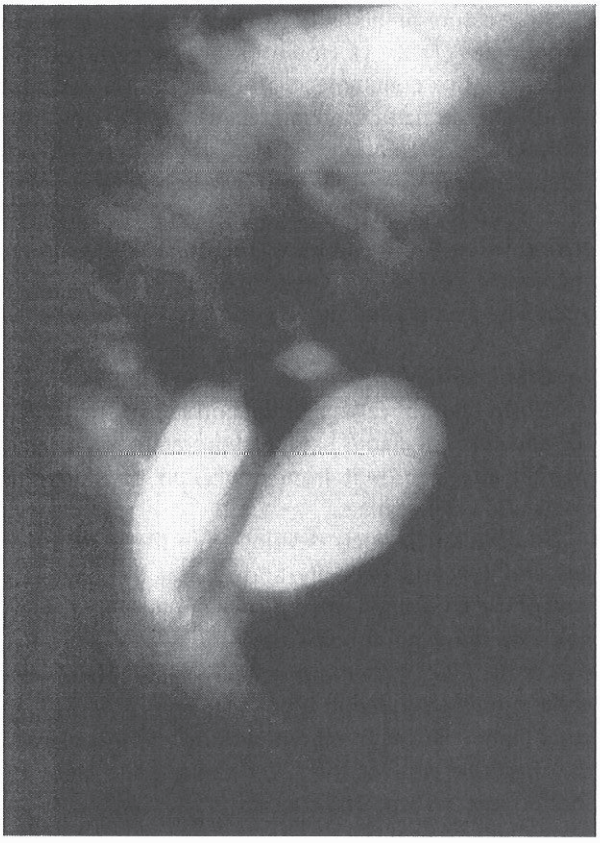

Figure 3. Lateral view of regression of hydronephroses 4 months after operation

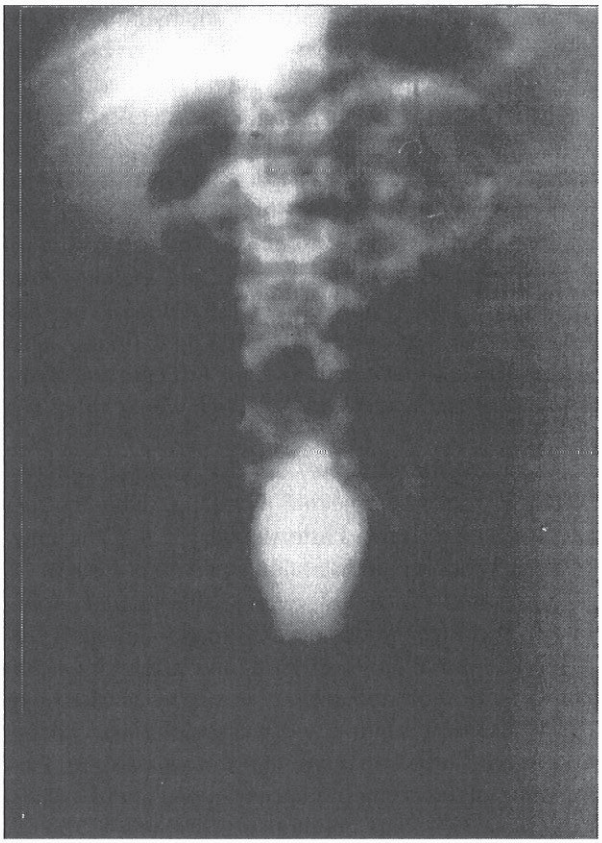

Figure 4. Postoperative vaginogram of case-3 showing normal size and diameter

by involution of the central cells of the vaginal cord in a caudal to cranial direction. Thus, the upper half to two-thirds of the vagina is formed by the Mullerian ducts and the lower portion by the UGS (5,10,11,12). The pathologic embryology of HMC focuses upon the stage of fusion of the uterovaginal canal with the sinovaginal bulbs (7). If the fusion stage does not occur, subsequent enlargement of the primitive vaginal plate does not happen, the urethra does not descend with vaginal plate and the vaginal lumen does not develop in its lowermost segment. Thus this developmental anomaly seems to be of UGS origin and hence the most common anomalies are those of the hymen and lower vaginal segment (1,5,8,11,12).

The accumulated fluid of newborns and infants with HMC comes from the cervical and vaginal glands activated by placental transfer of maternal estrogens. The question arises as to why the more familiar form of vaginal outlet obstruction, namely an imperforate hymen becomes apparent as hematocolpos only when menstruation begins at puberty. In other words why in one infant does HMC develop in infancy while in another with a comparable vaginal outlet obstruction, the condition becomes apparent only when menses begins? A possible explanation is that ,there is an individual variation in the amount of estrogens produced by child bearing women. In support of this theory, it has been pointed out that some infants of both sexes have transitory gynecomastia and "witches milk" at birth (5).Profuse vaginal discharge in newborn, even bloody, is well known. On the other hand, fluid accumulation in the proximal vagina of the newborn and infant with vaginal outlet obstruction may also be the result of estrogenic receptors, an issue yet to be investigated.

A 35% overall mortality and a 50% operative mortality, mostly being due to improper surgical treatment or unrecognized HMC has been reported (6). Review of the English literature revealed 147 cases of HMC in infants, excluding the ones due to persistent cloaca, between 1940 and 1986. Sixtythree were high vaginal atresia due to transverse vaginal septum (1, 2, 4, 6, 7, 8, 9). Incision of high vaginal septum

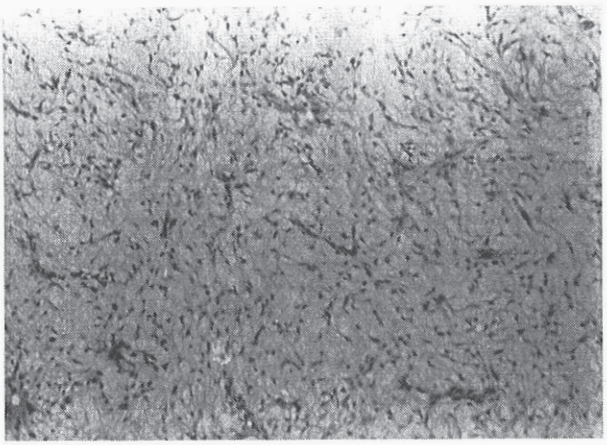

Figure 5. Lipoblasts having atypical nucleus and mitosis between branching rich capillary network in a liposarcoma association in a child with hydrometrocolpos

and simple abdominoperineal drainage form a common urethrovaginal canal in place of the UGS, which has not allowed adequate drainage from either the newly opened vagina or the bladder. "Retrograde urination" into the vagina may be due to the external urethral sphincter encircling the UGS and the presence of female type hypospadias. Infected vaginal secretions are not allowed to drain freely, urinary and genital tract infections persist, and the usual septic course results (7).

The infants with HMC in this series have been successfully managed with abdominoperineal vaginal pull-through technique. The hydronephroses and hydrourethers disappeared in two months. Early dilatation of the lower portion vagina for 6 months postoperatively prevents stricture formation. Hypertension in the first case persisted for only two months. None of the cases have urinary incontinence.

Genitourinary tract malformations has a high association of gonadal and renal neoplasia. However in the presented limited series we have encountered a liposarcoma. This association has not been reported previously.

CONCLUSION

Every effort to successfully diagnose HMC before surgery with a thorough physical, rectal and external genital examination is a prerequisite in order to avoid unnecessary hysterectomies and vaginectomies. Intravenous pyelography and ultrasound examination are essential in preoperative evaluation and postoperative follow-up due to high frequency of genitourinary tract tumors in infants and children. Ultrasound of the mass will reveal its cystic nature and an enlarged and opened cervical ostium. A vaginal pull-through operation is the best treatment for the patients with high vaginal obstruction. This is especially so when the urethral opening is high in the UGS. These cases as in the other urogenital malformations should have a specific fallow-up for renal, gonadal and soft tissue sarcomas.

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IMMUNOHISTOCHEMICAL EXPRESSION OF NEURON-SPECIFIC ENOLASE AND CHROMOGRANIN A IN PROSTATIC ADENOCARCINOMA

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Erol Özdiler • Orhan Göğüş

SUMMARY

The reported incidence of neuroendocrine differentiation in prostatic carcinoma has steadily increased from 10 to 100% depending on the method used to demonstrate these cells. In this study we determined the incidence of neuroendocrine differentiation, as determined by neuron-specific enolase (NSE) and chromogranin A (chrA) preparations, in prostatic carcinoma patients and its correlation with subsequent tumor progression.

Tissue samples from 36 sequentially selected newly diagnosed prostatic carcinoma patients were studied for NSE and chrA expression. All patients were followed for at least 1 year or until death.

Only one of the 36 patients was found to be positive for NSE and chrA (2.8%). This patient had a T3N0M0 disease with a Gleason score of 6 and is still alive without disease progression with a follow-up period of 37 months. Of the remaining 35 patients who were negative for NSE, 27 had a Gleason score of ≥ 7 and 8 had a Gleason score of 6. Nine of these 35 patients died of progressive disease (range 3 to 46 months) whereas 26 were alive without disease at last follow-up (range 12 to 33 months).

The current study showed that the incidence of neuroendocrine differentiation, as demonstrated by immunohistochemical NSE and chrA expression is very low in prostatic carcinoma patients. However to draw any definitive conclusion a study with a large number of patients is necessary.

Key words: *Prostatic neoplasms, neuron-specific enolase, chromogranin A, neurosecretory systems, adenocarcinoma*

ÖZET

Prostat adenokanserinde nöron spesifik enolaz ve kromogranin A'nın immunohistokimyasal ekspresyonu

Prostat kanserinde nöroendokrin diferansiyasyon insidansı, kullanılan yönteme gere değişmekte ve bu isidans %10-100 arasında bildirilmektedir. Bu çalışmada nöron spesifik enolas (NSE) ve kromogranin A (chr A) kullanılarak prostat kanserli hastalarda nöroendokrin diferansiyasyon insidansı tayin edildi ve tümör progresyonu ile krolasyonu araştırıldı.

Yeni tanı konulmuş prostat kanserli 36 hastanın doku örneklerinde NSE ve Chr A ekspresyonu çalışıldı. Tüm hastalar en az 1 yıl ya da ölüme kadar takip edildi.

Sadece 1 hasta da NSE ve Chr A pozitif bulundu (2.8%). Bu hastanın T3NOMO evresinde Gleason skoru 6 olan tümörü olup, 37 aylık takibinde halen progresyonusuz olarak hayattadır. NSE negatif olan 35 hastanın 27'sinde Gleason skoru >7 ve 8'sı (12-33 aylık takipte) hastalıksız olarak hayattadır.

Bu çalışmada, immunohistokimyasal olarak NSE ve Chr A ekspresyonu ile gösterilen nöroendokrin diferansiyasyon insidansı prostat kanserli hastalarda çok düşük bulunmuştur. Bu konuda daha fazla sayıda hasta ile yapılmış çalışmalar ihtiyaç vardır.

Anahtar kelimeler: *Prostat kanseri, nöron spesifik enolaz, kromogranin A, nörosekretuar sistem, adenokanser*

The epithelial cell component of the prostate consists of secretory and basal cells, along with highly specialized neuroendocrine cells (1,2). Neuroendocrine cells have cytoplasmic secretory granules. Although it is speculated that they play a role in the regulation of growth and differentiation their functional role in the prostate is unknown (3,4,5). The reported incidence of neuroendocrine differentiation in prostatic carcinoma has steadily increased from 10 to 100% depending on the method used to demonstrate these cells (1,3,6). Some studies have suggested that the presence of neuroendocrine differentiation in primary

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prostatic carcinoma appears to correlate with a poor prognosis (3,6,7) but this has been refuted (8,9).

Neuron-specific enolase (NSE) is an isoenzyme of the glycolytic enzyme enolase that is identified in neuroendocrine cells (10). ChrA also identifies neuroendocrine cells. Prostatic adenocarcinoma with neuroendocrine differentiation can show immunoreactivity with the antibody for NSE (1,4,7). The objective of our study was to assess the incidence of neuroendocrine differentiation in prostatic adenocarcinoma by NSE and chrA immunostaining and its relationship to tumor progression.

MATERIALS AND METHODS

Thirty-six patients with histologically confirmed adenocarcinoma of the prostate were selected sequentially from the hospital records at this institution from May 1992 to March 1995. Mean patient age was 64 years (range 54 to 76). These patients records met the following characteristics for inclusion in this study: (a) no clinical history of androgen-deprivation therapy, chemotherapy or radiation therapy (b) formalin fixed paraffin embedded tissue from a needle biopsy or a radical retropubic prostatectomy specimen available for immunostaining (c) clinical follow-up after treatment for at least one year or to date of death.

These newly diagnosed, untreated prostate cancer patients had been staged before any treatment using a combination of digital rectal examination, serum PSA measurement, biopsy with tumor grading and transrectal ultrasound, chest X-ray and bone scanning. Tumors were staged according to the 1992 TNM classification (11) . The clinical stage of the disease in these 36 patients was T2N0M0 in 17, T3N0M0 in 5 and T2-4NXM+ in 14. Of 17 patients with clinically organ-confined prostatic carcinoma 13 underwent radical prostatectomy and 4 received radiation therapy. The remaining 19 patients with locally advanced or metastatic prostate cancer received androgen-deprivation therapy.

In the biopsy specimens, the block containing the largest amount of the tumor was stained taking care to preserve the identity of each specimen. Hematoxylin and eosin (H&E) stained sections from each patient with radical prostatectomy were reviewed to determine areas of malignancy to be included and in these patients the radical prostatectomy and the preoperative biopsy specimens were studied. The histologic specimens were graded according to the Gleason system. Gleason scores were determined by adding the grades of the predominant two Gleason patterns. For patients with multiple biopsies in whom different scores were reported, the highest score was used for data analyses.

To determine the presence of neuroendocrine staining in the prostatic carcinomas, the NSE and chrA stains were reviewed by light microscopy by pathologist who were blinded to the results of the clinical follow-up. For immunohistochemical studies, 5mm thick sections were obtained from representative paraffin blocks and placed on adhesive slides. Immunostaining with an antibody against NSE and chrA (Dako Corp., Carpinteria, CA, USA) was performed using streptavidin-biotin peroxidase method.

The negative controls were performed by replacing the primary antibody by PBS (Phosphate Buffered Saline). The positive controls were done by using ganglion sections for NSE and chrA.

RESULTS

Thirty-five of the 36 patients were shown to be negative for NSE and chrA. Only one patient was positive for both NSE and chrA. In this case NSE positive cells identified occasionally (Fig.1). This patient had a T3cN0M0 disease with a Gleason score of 6. He received androgen-deprivation therapy (orchiectomy+flutamide, 250mg X 3/day) and is still alive without clinical evidence of progression. Follow-up period of this patient was 37 months.

Of the remaining 35 patients who were negative for NSE and chrA, 27 had a Gleason score of ≥ 7 and 8 had a Gleason score of 6. Nine of these 35 patients died of progressive prostatic carcinoma. Median follow-up for these 9 patients was 27 months (range 3 to 46 months). Of the remaining 26 patients, 18 were ali-

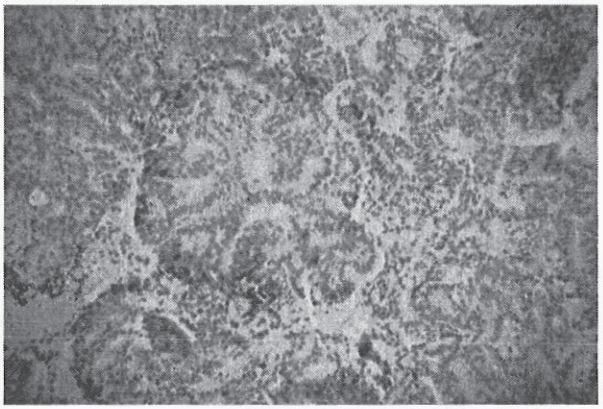

Figure 1. NSE positive cells in dark brown (X200)

ve with disease whereas 8 patients (radical prostatectomy patients) were alive without disease at last follow-up (range 12 to 33 months).

DISCUSSION

In addition to the basal and secretory cells, neuroendocrine cells (endocrine-paracrine cells) of the prostate constitute a third population of highly specialized epithelial cells in the prostate gland (1,4,6). The use of increased number of neuroendocrine markers, such as NSE, chromogranins, calcitonin, seratonin has steadily increased the incidence of neuroendocrine differentiation in prostatic carcinoma (1,6,12). Little is known of the functional role of the these cells, but they probably play a significant role during prostatic growth and differentiation as well as regulating the secretory process of the mature gland (1,6).

NSE, an isoenzyme of the glycolitic enzyme enolase represents a highly specific marker of neuroendocrine cells (13). chrA is an acidic protein of uncertain function that constitues more than half the weight of many types of neuroendocrine secretory granule(14).Although by using a variety of more sensitive markers detection of neuroendocrine cells has steadily increased up to 100% (13) , the incidence of NSE positive carcinoma of the prostate has been shown to be ranging from 24% to 48.4% (1,7,15). Furthermore in metastatic lesion of prostatic carcinoma 25% has been reported to contain NSE immunoreactive cells. On the other hand, in our study only 1 out of 36 prostatic carcinoma cases (2.8%) has been found to be positively stained for NSE and chrA. We have used chrA to be sure of presence of neuroendocrine cells in NSE positive case. It is hard to explain these highly different rates of NSE positive cells in prostatic carcinoma cases. However, in 1994 Bostwick at al. reported that neuroendocrine differentiation was downregulated in prostatic carcinogenesis and demonstrated that neuroendocrine cell immunoreactivity was greater in prostatic intraepithelial neoplasia than in carcinoma, but both have fewer immunoreactive cells than benign epithelium (4). So although our incidence of 2.8% NSE positivity rate in 36 prostatic carcinoma cases is the lowest rate reported in the literature, it might be due to the high number of patients with a Gleason score of ≥ 7.

It has been reported that, the most common pattern of neuroendocrine differentiation in prostatic carcinoma is conventional adenocarcinoma of the prostate with focal neuroendocrine differentiation (6,7). In some studies this focal neuroendocrine differentiation has been shown to portend a poor prognosis (7,16,17) whereas in some other recent reports no significant correlation has been found (1,8,9). As we had only 1 NSE and chrA positive patient in our study, it is hard to make a correlation between NSE and chrA positivity and subsequent progression of prostatic carcinoma.

CONCLUSIONS

The current study showed that the incidence of neuroendocrine differentiation as demonstrated by NSE preparations is very low in prostatic carcinoma patients. However, to draw definitive conclusion a study with a large number of patients is necessary.

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ATTITUDES TOWARDS ASSISTED SUICIDE (EUTHANASIA) IN TURKIYE*

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SUMMARY

Due to the rapid technological developments, life sustaining technologies began to be used more efficiently in Turkiye. This increasing competence prompted up assisted suicide debate amongst academics, media and consequently the society in general. As a secular Muslim country, which is a seldom fact, the debate has an interesting content in Turkiye. Islam, on the one side, has a clearcut negative approach towards suicide in general. On the other hand, the secular government accepted many procedures in accordance with the scientific developments, like abortion, which can hardly cohere Islamic arguments.

Turkiye is also in a continious alternation both socially and economically. Many traditional practices have changed, the practices about illness and death are among those. Physicians who are also one of the components of the society reflect altering attitudes very clearly. In this article, our aim is to emphasize the changing attitudes in the society and review some data about the attitudes of Turkish physicians towards assisted suicide.

Key words: *Assisted suicide, medical ethics, psychiatry*

ÖZET

Türkiye'de hekim yardımlı özkıyıma (Ötanazi) yönelik tutumlar

Ülkemizde hızlı tekonoljik gelişmelere bağlı olarak yaşam destek sistemleri de daha etkili bir biçimde kullanılmaya başlanmıştır. Artan bu yetkinlik hemek yardımlı özkıyım tartışmasının hem akademisyenler ve meday, ve hem de buna bağlı olarak tıplum genelinde başlamasını sağlamıştır. Hem müslümanların çoğunlukta bulunduğu hem de laik bir ülke olmakla nadir bir olğu durumnda bulunan ülkemizde tartışmanın içeriği ilginç boyutlardadır. Bir yanda genel olarak özkıyıma açıkca karşı olan İslam, öte yanda abortus olgusunda olduğu gibi, bilimsel gelişmelerle koşut olarak İslamla uyum göstermesi olanaksız olan birkçok yöntemi kabul eden laik yönetim bulunmaktadır.

Tüm bunlara ek olarak Türkiye, hem toplumsal hem de ekonomik açıdan sürekli bir değişim içinde bulunmaktadır. Hastalık ve ölümle ilgili olanlar da içinde olmak üzere pek çok geleneksel uygulma değişmiştir. aynı zamanda toplumun birer öğesi durumunda olan hekimler, tutumlardaki bu dönüşümü en açık biçimde yansıtmaktadırlar. Bu makalede amacımız toplumdaki bu değişimleri vurgulamak ve Türk hekimlerin hekim yardımlı özkıyım konusundaki tutumlarını gösteren verileri gözden geçirmemektir.

Anahtar kelimeler: *Yardımlı intihar (ötanazi), medikal etik, psikiyatri*

Türkiye is a rapidly developing country. Due to the population explosion and high rate of internal migration, there is a rapid urbanisation. Rapid urbanisation, industrialisation and improvement in the relations with the western world shake social and cultural value systems, traditional practices, beliefs, attitudes and behaviour in the Turkish society. In addition, in Türkiye there is a great difference between the life standards of the eastern and western parts of the country, inevitably between the level of the medical technology aswell. Despite many rapid changes, some beliefs and attitudes have remained the same.

Muslims constitute 90% of the total population and Islam's approach towards death is quite clear. Allah is the creator and the master of life and death, so ending life according to the personal decision or asking some-

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body to do it instead should be regarded as an attempt to share Allah's power. Consequently this practice is assumed to be an unforgivable sin. According to Koran, human wish for his own death is forbidden. Suicide is a drastic sin, and because of its severity no funeral prayer is allowed for suiciders, which means that they can never be the recipients of Allah's final forgiveness(1).

In Türkiye, discharging terminally ill patients from the hospital according to their relatives wishes or on his own request, even without his physician's consent, is a common procedure. Death in the hospital is usually accepted as an alien condition and tried to be avoided. Patients prefer to be at home, in their beds and surrounded by their loved ones when they are dying. Because of this preference, approximately 50% of the dying patients meet death at home(1). It is sometimes voluntary, but sometimes it is involuntary for the patient. As hiding the deadly truth from the patient is a common procedure in the clinics, most of the patients do not know that they are discharged from the hospital not because they have cured, but because they have entered the terminal phase of the disease. As the daily care at home is quite insufficient, this decision shortens patient's life however(2). That is why we claimed that this procedure can be regarded as passive involuntary euthanasia.

As we mentioned above, patients and their relatives do not want to be informed about the diagnosis when it is a fatal and hopeless one. Many physicians approve this behaviour and found it logical, somewhat as they believe that this attitude helps patients in preserving their hope(2). In Türkiye, people widely believe that there is a hope till the moment of death(2). This way of thinking makes it easier to wait for death. It is less painful for the patient, relatives and friends, although everybody knows that the death is inevitable.

The concept of "euthanasia" entered the agenda of Türkiye in the last twenty-five years. As a result of technological and medical developments, the discussion began as it was in the rest of the world. Physicians, patients, relatives, insurance companies and lawyers met the dilemma from day-to-day, and the mass media began to put it on the agenda more and more. A lot of discussions have taken place. There is an important pressure which forces the state to formulate some attitudes about euthanasia.

The mass media has played a very significant positive role in the transformation of Turkish society and has begun to be called as the fourth power by the sociologists. Although it helps us in discussing the important facts about euthanasia in Türkiye, sometimes it distorts the reality according to the financial concerns, such as the concerns about the circulation of the newspaper. The death of Cees Van Mendel de Joode from Netherlands (1994) and Roman Sampedro from Spain (1998) was widely discussed by reporters and commentators. This kind of news caused some changes in the discussion of the issue and the public debate entered different phases like joustic, religious, ethical and medical. Last two cases were those of two young women, Bahar and Rabia. Those were the Turkish cases which did not end up in the court, but died because of some extraordinary medical interventions. One of them, namely Bahar, had a quadriplegia which was caused by a car accident. After her request for aid-in-dying, she had become a flash news. This case made euthanasia a hot topic again in Türkiye. She did not receive that aid which she had searched for, but died after a huge debritement operation.

Medical doctors and academics are also interest in euthanasia. There are different studies on euthanasia in Türkiye. Especially in the last few years academics are paying more attention to the subject.

In 1990, Sayıl et al. performed a study on the attitudes of psychiatrists towards euthanasia (this study was presented at the 3rd European Symposium of Suicide in Bologna). The most important result of this study was that the younger psychiatrists (less than ten years of professional experience) seemed more tolerant towards euthanasia, while the older ones refused it totally(3).

510 medical students and physicians are interviewed about euthanasia by Gündüz et al. in 1996. One third of the subjects did not have enough information about euthanasia, while 63,72% of them supported its application; but still 68,82% of them refused to take responsibility in the procedure even if the process is approved by law. Opinions of the subjects who are for and against the idea were determined that although passive euthanasia is not legal, it is currently being applied when it seems necessary (4).

Another study performed by Oguz et al. in 1996 explored the clinicians attitudes towards euthanasia. 1343 clinicians responded to a questionnaire about patients' requests for euthanasia. According to the results, 75,3% of the clinicians were found to be willing to take active steps to hasten death. 26% of the respondents agreed with the idea that euthanasia is not ethically justifiable, whereas 63,9% reported that they could feel comfortable about euthanasia if the decisi-

on was made and the procedure was performed by a committee (Oguz et al. 1996)

There are many other studies performed especially by the medical staff, most of them concluded with the similar results.

As a result, it can be claimed that the euthanasia debate in Türkiye most likely will stay within the limits of academic societies for a few more years. But as the transformation of Turkish society appears to be a rapid one, many of the past predictions turned out to be wrong. It is very clear that economical, social and technological developments put considerable pressure on the state for a legislative arrangement about euthanasia, so that it can be accepted legally. It happened in the same way for abortion, organ transplantation, genetic technologies and in vitro fertilisation in the past. As a secular state, Turkish legal system is both rational and open to the changes, after considering the modern requirements. In order to lead a healthy and productive debate, more conceptual knowledge and statistical data is needed as well as the discursive contributions.

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ABNORMAL UTERINE BLEEDING IN ADOLESCENTS: A CASE REPORT

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SUMMARY

Abnormal uterine bleeding is one of the most common reasons for gynecologic consultation in adolescents. Symptoms range from the average menstrual pattern to life-threatening hemorrhage. Whatever the seriousness of symptoms, it is a subject of great concern for the patient, her parents and the physician, and it needs attentive management. A case of 15 year old adolescent with abnormal vaginal bleeding who has been evaluated and managed in Ankara University School of Medicine, Department of Obstetrics and Gynecology , was presented in the view of literature.

Key words: *Adolescent, abnormal uterine bleeding, treatment*

ÖZET

Adölesanlarda anormal uterin kanama

Adölesanlarda, anormal uterin kanama jinekolojik sorunların en önemlilerinden birisidir. Semptomlar, miktarı hafifçe artmış menstrual kanamadan hayatı tehdit eden kanamaya kadar değişebilir. Fakat semptomların şiddeti ne olursa olsun hem adölesan hem de ailesi için üzerinde önemle durulması gereken bir durumdur. Bu makalede, anormal vaginal kanama şikayetiyle Ankara Üniversitesi Tıp Fakültesi Kadın Hastalıkları Ve Doğum ABD.' na başvuran ve tedavi gören 15 yaşında bir adölesan olgu literatür eşliğinde değerlendirilmiştir.

Anahtar kelimeler: *Adölesan, anormal uterin kanama, tedavi*

Abnormal uterine bleeding is one of the most irritating problem for gynecologic consultation in adolescents and needs to be evaluated seriously. It may be characterised by excessive bleeding during the menstrual period (menorrhagia), by frequent and irregular bleeding (metrorrhagia), or a combination of both (menometrorrhagia). Abnormal uterine bleeding may occur in women of all ages; it is a particularly common for adolescents. As many as 95% of cases of abnormal vaginal bleeding in adolescents are caused by dysfunctional uterine bleeding (DUB) (1). DUB, by definition, occurs on the basis of anovulatory cycles, and its diagnosis depends on exclusion of other causes. Therefore potential causes of uterine bleeding must be ruled out systematically. Although it accounts for the greatest number of incidences caused by an immature hypothalamic-pituitary-ovarian axis, one must consider other causes like pregnancy, abnormalities of the uterus or vagina, coagulopathies and other systemic disorders (Table 1).

Pregnancy-related complications are common in adolescents and should be excluded even in the adolescent who denies sexual activity(2). A common uterine cause of abnormal bleeding in teens is endometritis, which is often caused by Chlamydia trachomatis or Neisseria gonorrhoeae infection (3). Though rare, benign and malignant conditions of the genital tract may be responsible for severe hemorrhage. Endometriosis may be associated with abnormal menstrual periods and should be considered, particularly if a patient complains of significant dymenorrhea (4) or chronic pelvic pain (5). Postcoital or self-imposed traumatic conditions and intravaginal foreign bodies also should be considered.

Coagulation disorders are probably the most common systemic condition associated with acute menorrhagia. The prevalence of a primary coagulation disorder in adolescents requiring medical admission for abnormal vaginal bleeding ranges from 20% in one study (6) to only 3% in another (7). Idiopathic thrombocytopenic purpura, von Willebrand disease, Glanz-

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Table 1. Differential Diagnosis Of Abnormal Vaginal Bleeding In Adolescents

Uterine causes	Systemic causes
	Endocrine abnormalities:
Anovulatory bleeding	Polycystic ovary syndrome
Endometrial polyps	Hypothyroidism
Fibroids	Hyperthyroidism
Arteriovenous malformations	Hyperprolactinemia
Chlamydia endometritis	Cushing disease
Uterine cancer (rare in adolescents)	Addison disease
	Premature ovarian failure
Intrauterine device	*Coagulopathies:*
Endometriosis	Von Willebrand disease
Vulvar and vaginal causes	Factor deficiencies
Trauma	Idiopathic thrombocytopenic purpura
Foreign body	Liver disease
Vaginitis	
Pregnancy-related complications	Renal failure
	Leukemia
Spontaneous abortion	Aplastic anemia
Complications of pregnancy termination procedures	Iron-deficiency anemia
	Medications:
Ectopic pregnancy	Hormones
Gestational trophoblastic diseases	Warfarin
	Anticonvulsants
Bleeding of the third trimester of pregnancy	**Benign and malignant tumors**
	Vagina, cervix, uterus, ovary

mann disease, thalassemia major, Fanconi anemia, leukemia, radiation and chemotherapy side effects, and some drugs (anticoagulants, aspirin, hepatotoxic drugs) are possible causes of deficient coagulation mechanisms. Von Willebrand disease is the most common bleeding disorder, affecting as many as 1% of the population, and may be missed unless specific tests for von Willebrand factor are performed (8). Other systemic conditions possibly associated with menorrhagia include thyroid dysfunction, diabetes mellitus, nutritional disorders, and hepatic and renal diseases. PCOS is the most common cause of persistent anovulation in adolescents and should be considered in any adolescent with hirsutism, acne, acanthosis nigricans (9). Finally, exogenous causes of vaginal bleeding include hormonal medications, such as depomedroxyprogesterone acetate or oral contraceptive pills (which patients may be taking without their parents' knowledge) (9).

CASE REPORT:

D.G. was a 15 year-old adolescent who presented with a chief complaint of irregular menses for the past 3 years. She had menarche at age 11 years, her periods were regular for 4 months at the beginning, but than she began to complain about menstrual irregularities. She had vaginal bleeding daily for the past 2 months. The bleeding was generally light, one ped for a day. But 3 days ago she had heavy bleeding. Her past medical history was unremarkable and there was no history of bleeding disorders. She takes no medications. She had no sexual intercourse. Medical history of the family was also unremarkable.

On physical examination, her pulse was 110 bpm, and blood pressure is 100/60. She had no hirsutism, acne, or acanthosis nigricans. Her thyroid was normal, her breasts were Tanner stage 5, and her pubic hair is Tanner stage 4. No speculum and bimanual vaginal examination was done as she was virgin, but her rectovaginal examination was normal.

Laboratory investigations except complete blood count was normal. She had a hemoglobin level of 6.9 gm/dL; hematocrit, 22.4%; white blood cell count, 6700/mL; and platelet count, 219000/mL. βhCG was negative. Her pelvic ultrasonography was normal. Investigations for bleeding disorders revealed no disease; PT: 13.5 sec. (11-15), aPTT: 27.25 sec. (24-36), INR: 1.15 (0.9-1.5), fibrinogen: 194.03 (200-400), D dimer: 50.94 (0-250), VWF: 112% (50-150).

On the first day of admitting to hospital she had 2 units of blood transfusion. Her tachycardia was subsided after blood transfusion. In order to rule out any vaginal pathology, vaginoscopy was performed but no pathologic condition was detected. Hence there was no cause of vaginal bleeding that can be proved by laboratory; the diagnosis thought to be dysfunctional uterine bleeding. She was placed on OCP, (Ovral ®), four pills a day for the first 3 days and than dose was decreased gradually. Oral iron supplementation was given also. She responded well to the OCPs and her bleeding subsided. On seventh day of admittion to hospital she was discharged without vaginal bleeding.

DISCUSSION

The evaluation of irregular vaginal bleeding should include history and physical examination, including the age of menarche, menstrual pattern, amount of bleeding, symptoms of hypovolemia, history of sexual activity, genital trauma, and any symptoms to suggest an endocrine abnormality or systemic illness. Postural vital signs should be obtained as objective evidence of hypovolemia, and a pelvic examination should be performed to rule out abnormal anatomy, trauma, infection, foreign body, and possibly a pregnancy-related complication. Pelvic ultrasonography can be helpful if there is a question of abnormal pelvic anatomy.

Laboratory evaluation always should include a pregnancy test and complete blood count. If a speculum examination has been performed, and no active bleeding seen tests for chlamydia and N. gonorrhoeae infection together with a Papanicolaou smear and a wet preperation to look for Trichomonas vaginalis infection should be performed (9). If there is a history of a very heavy period with menarche or repeated prolonged or heavy menses, bleeding disorders should be investigated. Evaluation of prothrombin time, partial thromboplastin time will provide a screen for bleeding abnormalities. Bleeding time and von Willebrand screening panel can be used to identify more specific coagulation disorders (10). Signs of androgen excess would indicate a need for investigation of polycystic ovary syndrome. A chronic history of irregular vaginal bleeding also warrants investigation of other causes of anovulation, including prolactinoma and endocrine abnormalities such as thyroid disease. A pelvic sonogram is indicated if a mass is palpated or if a bimanual examination cannot be performed and the bleeding does not respond to hormonal therapy. The need for additional diagnostic studies including vaginoscopy depends on the clinical assessment of each patient.

The aim of therapy should be to control bleeding, restore adequate intravascular volume, correct anemia, treat any underlying conditions, and prevent recurrence. Method and intensity depend on the severity of hemorrhage (9). When other possible causes for an adolescent's abnormal vaginal bleeding have been excluded and the diagnosis of DUB has been made, physician must decide how to treat these patients. The following classification and treatment plan is one way to manage dysfunctional uterine bleeding in adolescents (Table 2), (11).

Observations, keeping a menstrual calendar and receiving information about normal physiology are appropriate management for mild dysfunctional bleeding. The use of nonsteroidal medications (NSAIDs) can decrease the amount of bleeding. Naproxen sodium, 275 mg every 8 hours during menses, has been shown to significantly decrease menstrual blood loss (12). With maturation of the hypothalamic-pituitary-ovarian axis, the bleeding should become more regular.

The aim of the treatment is to stop the bleeding with hormonal medication using estrogen and progesterone or progesterone alone for moderate dysfunctional bleeding. Combined oral contraceptives (OC) are a convenient way to administer these hormones. Combination oral contraceptives are more effective than progesterone in stopping active bleeding. The use of an oral contraceptive with the progestin levonorgestrel or norgestrel is preferable because it exhibits a stronger progestational effect on the endometrium. Depending on the amount of bleeding, there are many ways to use OCs in the treatment of abnormal vaginal bleeding (11). Iron therapy should be included in all therapeutic regimens to correct the anemia. Adolescents in need of birth control obviously benefit from oral contraception. If a patient is unwilling or unable to take daily OCs and is not sexually active, an alternative; intermittent oral medroxyprogesterone acetate, 10 mg daily for 10 to 14 days every month or norethindrone acetate, 5 mg to 10 mg daily for 10 to 14 days, can be given. Regular follow-up is essential, and these patients should be seen again within 3 months. For patients whose hemoglobin level has decreased to less than 10 gm/dl but who are asymptoma-

Table 2. Classification And Treatment Of Dysfunctional Uterine Bleeding In Adolescents

Group	Management
	Reassurance
Mild Dysfunctional Bleeding	Menstrual calender
Menstruation is mildly prolonged	Iron supplement
Interval between menses may be shortened	NSAID
Hemoglobin value is normal (>12 gm/dl)	Reassurance
	Reevaluation
Moderate Dysfunctional Bleeding	Menstrual calender
Menses is prolonged and heavy	Iron supplement
Interval between menses is shortened	Cyclic progesteron or OC
Mild anemia (10-12 gm/dl)	Reevaluation
	Transfusion
Severe Dysfunctional Bleeding	Fluid replacement
Prolonged and heavy menstrual bleeding	Hormonal hemostasis (IV estrogen)
Hemoglobin level below 9gm/dl	Progestins
Clinical signs of hypovolemia	D/C
	OC continued 6-12 months

tic and not actively bleeding, treatment with a low-dose estrogen-progestin OC is indicated, together with iron supplementation therapy

Adolescents with severe dysfunctional bleeding need to be admitted to a hospital if there are clinical signs of hypovolemia. Laboratory tests for coagulation defects are indicated. Initial treatment is usually medical rather than surgical. Transfusion is necessary only if the bleeding cannot be stopped quickly or the hemoglobin value is dangerously low. The goal of therapy is to stop the hemorrhage with estrogen and to stabilize the endometrium with progestogens. OCs may be effective, one tablet every 4 hours, should be started along with an antiemetic medication. When the bleeding stops or decreases appreciably, oral contraceptives are tapered gradually for the next 7 days and then continued at a rate of one pill per day for 21 days. Withdrawal bleeding occurs after the discontinuation of treatment. The patient should be informed that this bleeding may be heavy but will be self-limited. If the patient cannot tolerate oral therapy, IV estrogen can be given at a dose of 25 mg every 4 hours, for not more than three doses. The major side effect of this therapy is nausea and vomiting, for which antinausea medications may be administered prophylactically. When the patient's bleeding has stopped, progesterone therapy needs to be added to stabilize the endometrium so the patient does not experience estrogen withdrawal bleeding. In our patient, though she has severe DUB with a hemoglobin level of 6,9 gr/dl; we prefered to use ovral 4 pills a day for the first 3 days, then continued with 3 pills/day for the next 3 days, and 2 pills/day for another 3 days and then one pill/day for 21 days. She did not need any antiemetic, and vaginal bleeding stopped on the 4th day of therapy. Surgical therapy with a uterine dilatation and curettage is rarely necessary in adolescents and is reserved for patients who fail medical treatment.

Once the patient's bleeding is controlled and her hemoglobin level has normalized, the patient can be allowed to have regular withdrawal bleeding. Therefore, it is advisable to continue therapy with low-dose birth control pills for at least 3 months. The adolescent in need of birth control can be continued on low-dose oral contraceptives. When the risk for unwanted pregnancy is not a concern, the best approach to administer oral progesterones cyclically. A rational regimen is to induce withdrawal bleeding every 6 weeks with a 10-day course of medroxyprogesterone acetate, 10 mg daily. This treatment is usually adequate to prevent endometrial hyperproliferation. Because it does not suppress the hypothalamic-pituitary-ovarian axis, it allows the development of regular ovulatory cycles. However, the patient may menstruate spontaneously between courses (13).

As conclusion; abnormal vaginal bleeding is one of the most common reasons for gynecologic consultation in adolescents. Symptoms range from the average menstrual pattern to life-threatening hemorrhage. Whatever the seriousness of symptoms, it is a subject of great concern for the patient, her parents and the physician, and it needs attentive management.

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CHERUBISM: REPORT OF A NONFAMILIAL CASE

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SUMMARY

Cherubism is a rare, benign fibro-osseous bone disease of the jaws. Disease is characterized by bilateral, painless enlargement of the jaws and cheek fullness. Jaws progressively enlarge until puberty and gradually resolves. This condition usually shows an autosomal dominant mode of inheritance with variable expression. A small number of sporadic cases without familial involvement have been reported. The purpose of this article is to report a case of cherubism without familial involvement in a patient with crescentic glomerulonephritis and to draw attension of pediatricians for this rare childhood disease.

Key words: *Cherubism, children, jaw enlargement*

ÖZET

Ailevi özellik göstermeyen bir olgu: Cherubism

Cherubism çenede görülen, benign fibro-ossöz bir hastalıktır. Bilateral yanaklarda dolgunluk ve çenede ağrısız büyüme hastalığın karakteristik bulgularıdır. Çene püberteye kadar progresiv olarak büyür ve bu dönemden sonra yavaş yavaş düzelir. Hastalık genellikle ekspresyonu değişken olan otozomal dominant kalıtımla geçer ancak familyal tutulum olmayan az sayıda sporadik olgu bildirilmiştir. Bu olgu sunusunda kresentik glomerulonefrit tanısıyla kliniğimizde izlenen ve daha sonra familyal tutulum saptanmayan cherubism gelişmiş olan bir hasta tanımlanmıştır.

Anahtar kelimeler: *Cherubism, çene büyümesi, çocuklar*

Cherubism is a rare, benign fibro-osseous disease of the jaws. It is usually inherited as an autosomal dominant trait with variable expression and penetrance which is usually 100 percent in males but 50-70 percent in females (1,2,3).

This disorder is characterized by symmetrical, painless enlargement of the jaws and cheek fullness producing cherub-like appearance. It progressively enlarges until puberty and gradually resolves thereafter (4 - 8).

Case Report

A 9-year-old girl who was being followed up with the diagnosis of crescentic glomerulonephritis (25 percent crescent formation) for the last 3 years, admitted to pediatric nephrology policlinic with a symmetric, bilateral, firm and painless enlargement of jaws. These findings were noticed two weeks ago. Her physical examination and laboratory investigation were normal except mild proteinuria(0.1 - 0.2 g / day) and microscopic hematuria during the follow-up period. Her parents were healthy and were not relatives. She had a healthy brother aged 16 year old.

Her growth was normal. A symmetric, bilateral firm and painless enlargement of the jaws and bilateral firm submandibular lymphadenopathy (2x2 cm) and irregular teeth appearance were detected. Physical examination was normal otherwise. Urinalysis revealed mild proteinuria (0.2 g / day). Complete blood count, serum electrolytes, urea, creatinine and albumin levels were within normal ranges. Serum calcium was 9.1 mg/dL, phosphorus 3.4 mg/dL, alkaline phosphatase 140 IU/L (normal 32-135 IU/L), parathyroid hormon 24 pg/mL (normal 12.0 - 72.0 pg/mL) . The patient was referred to the department of oral and maxillofacial surgery to further examination of the jaws. Expansion of the alveolar process and ascending ramus, migration of the teeth and limited movements of the tongue were detected in intraoral examination.

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In radiographic examination right and left mandibular corpus, ramus and the coronoid process were involved with a diffuse radiolucency which continued up to the condylar column and an improper trabecular structure was also observed. Total body scanning was normal except bilateral jaw lesions. The symphisis of mandibla was not affected but there was root resorption in the right and left second molars. Giant cell granuloma was diagnosed in the histological examination of incisional biopsy material. In order to facilitate eating and speaking functions and tongue movements an operation was performed. Mandibular mass was removed by curettage. The specimen was purple-brown in colour with firm consistency in macroscopic investigation. Histologically, the ground tissue of the lesion was formed of connective tissue where some of the cells were swollen and some were spindle-like. In some regions, groups of cells formed loose, haemorrhagic nodulations (Fig 1), containing focal siderophage groups and a sparse mononuclear cell infiltration. Multinucleated giant cells of osteoclast type were predominant almost in all regions. The histological diagnosis was giant cell granuloma and Cherubism was diagnosed with clinical, laboratory and histological findings. She has been followed-up for three years and her findings were not recurred.

DISCUSSION

Cherubism usually shows an autosomal dominant mode of inheritance with variable expression.A small number of cases without apparent familial involvement have been reported. It was difficult to assess whether these represent spontaneous mutations because of the variable degree of the expressivity of cherubism and its tendency to resolve (2, 3, 6, 7, 9, 10).There was no familial involvement in this present case either.

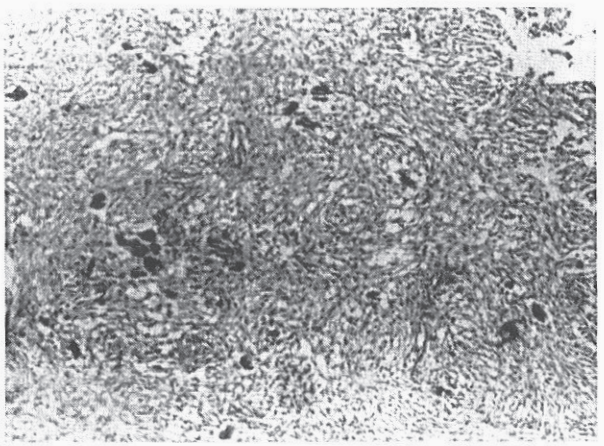

Figure 1. Giant-cell granuloma in fibrocellular stroma (x 100 Hem.eos.)

Bilateral expansion of the mandible and/ or maxilla are the important findings of disease but some patients with unilateral involvement have been reported. Maxillary involvement may cause a thin band of sclera to be exposed between the iris and the lower eyelid, resulting in characteristic "raised to heaven" appearance of the eyes. The most common site of occurrence is the mandible , particularly the ascending rami, the retromolar area and the area around the molars. The coronoid process can also be involved but the condyles are always spared (2,5).

The diagnosis is based on clinical findings and biopsy is generally not necessary. Cherubism can be distinguished from the other giant cell lesions with the combination of following clinicopathologic features. 1- bilateral jaw lesions, 2- exclusive occurrence in the jaws, 3- characteristic cherubic face, 4- involution at puberty, 5- high incidence of bilateral submandibular lymphadenopathy, 6- multiple,well defined multilocular radiolucencies of the jaws, 7- expansion of the alveolar process and ascending ramus, 8- affected parents or siblings (1,11).The presented case had almost all of these criteria except the familial involvement and the diagnosis was confirmed histologically.

Laboratory data are usually within normal limits, although an increase in alkaline phosphatase may occur when the disease is extensive (9).The radiographic appearance is multilocular,bilateral radiolucency that does not affect the mandibular condyle (4,5).Computed tomography and magnetic resonance imaging can contribute to the diagnosis. (8). The radiographic appearance and clinical history are characteristic findings for the diagnosis which is confirmed by histology showing multinucleated giant cells and vascular spaces within a fibrous connective tissue (7). Similar histologic findings are found in central giant cell granuloma, Brown tumor of hyperparathyroidism and giant cell tumor (4,7,11). Brown tumor can develop in patients with chronic renal failure as a result of secondary hyperparathyroidism (12,13) neither of which was present in this patient . Central giant cell granuloma can be excluded on clinical grounds because it is not a bilateral condition and does not regress in adulthood and has a predilection for the anterior mandibq. A distinguishing feature of many central giant cell gra-

nulomas is the presence of bony septa or trabecula within the lesions (4,5,14). Giant cell tumor is unusual in the jaws(2,7).

Generally lesions of cherubism resolve spontaneously after puberty and surgical intervention is not necessary in the absence of secondary disturbance. Surgical intervention must be based on the need to improve function, prevent debilitation and aesthetic consideration (3,5,8,9).

As conclusion, this childhood disease should be known by pediatricians for the diagnosis and treatment of patients.

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INTRADUCTAL PAPILLOMA IN INFANCY: A CASE REPORT AND REVIEW

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SUMMARY

A 3-year-old girl was admitted with a bloody nipple discharge persisting for 5 months An incisional biopsy had been taken and histology demonstrated ductal structures with cystic dilatations and wide lumens with an epithelial proliferation defined as intraductal papilloma. The patient was discharged on the operation day. She has had no further bloody discharge on 8 months of follow up.

Follow up with careful physical examination is essential for breast masses in children; when the mass is persistent, enlarging or symptomatic, surgical excision is advised. Intraductal papillary tumors which originate in the large and peripheral ducts are seen generally with no evidence of palpable mass but a bloody or yellowish green nipple discharge making a distinction between benign and malign lesions. After the determination of the origin, the excision of the papilloma should be performed.

In early years of life, intraductal papilloma may develop in females. Since malignancy is extremely low, they are generally managed conservatively. However management is still controversial. This case is presented to enlighten the issue.

Key words: *Intraductal papilloma, children*

ÖZET

Süt Çocuğunda İntraduktal Papillom: Bir Olgu Sunumu ve Tartışılması

Memebaşından 5 aydır devam eden kanlı akıntı nedeniyle kliniğimize başvuran 2 yaşındaki bir kız çocuğunda eksizyonel biyopsi yapılmıştır. Histopatolojik ve sitolojik incelemesinde, duktal yapılar içerisinde kistik dilatasyonlarla birlikte epitelial proliferasyon görülmüş; intraduktal papillom olarak tanımlanmıştır. Ameliyat sonrası 8 aylık kontrol süresinde hastanın ailesinde kaygılara yolaçan kanlı akıntı gözlenmemiştir.

Meme tümörleri çocukluk çağında nadir de olsa görülebilir. Malignite riski düşük olduğu için genellikle konservatif yaklaşım tercih edilir. Ancak bazı durumlar cerrahi tedaviyi gerektirebilir. Bu olgu çocukluk çağında memede saptanan tümörlere tanı ve sağaltım yaklaşımının tartışılması amacıyla sunulmaktadır.

Anahtar kelimeler: *Intraduktal papilom, çocukluk çağı*

Breast disorders seen in adult women may also occur early in life. In the diagnosis and treatment of these disorders in peadiatric and adolescent patients relative frequencies, natural history of these conditions and so the physician's approach differs from adults.Intraductal papilloma is one of the rarest breast disorders observed in peadiatric patients, espeacially infants. Since malignancy is extremely low, they are generally managed conservatively. However management is still controversial.

Case Report: A 3-year-old girl was admitted with a bloody nipple discharge persisting for 5 months. Through the physical examination right breast bud was non-palpable, left one was enlarged, and in 0,5 cm of diameter. Bloody discharge was observed when upper lateral quadrant of breast bud was palpeted. However no masses or calcification were detected in ultrasound and X-ray. Cytology repeated 4 times in a month indicated *class II cells and intra ductal papilloma* with a microscopic scene of erythrocytes, neutrophiles, hemosiderine phagosited macrophages with a papillomatous pattern of small clusters (Figure 1).

Enlarging of the breast bud and persisting bloody discharge forced us to take an excisional biopsy from upper lateral quadrant of breast bud. Histology demonstrated ductal structures with cystic dilatations and wide lumens with an epithelial proliferation defined as *intra ductal papilloma* (Figure 2).

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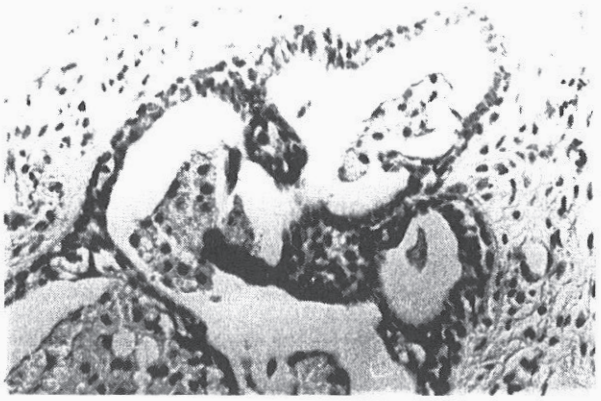

Figure 1. Papillomatous epithelial cell cluster with bland chromatin from nipple discharge in May-Grünwall- Giemsa stained cytology scene (X 1000)

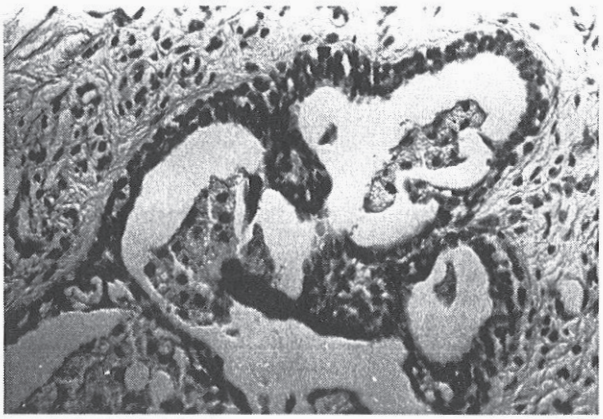

Figure 2. Intraductal papillary projection of proliferated duct epithelium and foamy macrophages in the lumen in H-E stained tissue section (X 200)

In the operation, the patient was discharged on the operation day, she has had no bloody discharge on 8 months of follow up.

DISCUSSION

Breast masses in children are not impossible to be encountered and are generally benign lesions. Causes of prepubertal breast masses are hemangioma, lipoma, papilloma, lymphangioma, solitary cyst, fibrosis, mastitis, hematoma, fat necrosis, tumors of adjacent structures, thelarche, and breast cancer(3).For differential diagnosis in childhood, mammography is not a suitable diagnostic method because of the size and architecture of the breast and poor image quality, so ultrasound is generally chosen, but is invaluable in assessing the clinical problems(6) A rising tumor from the chest wall, or ribs are to be distinguished by plain radiographs and computed tomography(3). A smear from the nipple discharge as we did in our case or, if possible, an aspiration biopsy from the mass will be helpful for diagnosis. Solitary intraductal papillomas are uncommon benign tumors of the breast forming in the large lactiferous ducts and may be associated with subareolar mass which rarely becomes large. Generally the admitting symptom is not the mass itself but a serous or bloody nipple discharge(1). Sometimes the mass and discharge are associated with localised pain. The subareolar mass is the dilation of obstructed duct, not the papilloma itself(2). Today it is thought that solitary intraductal papillomas do not undergo malign transformation, but there are rare reports of solitary intraductal papillomas occuring adjacent to breast carcinoma whose pathogenesis is unclear(7, 8). If multiple independent intraductal papillomas are present, there is a risk of malignancy(1). Although many authors advise to avoid from biopsy because the excision of child's breast bud may lead to scarring, and iatrogenic unilateral amastia(3), others advise to excise the mass if it's enlarging or symptomatic and skin changes are observed(4). intraductal papilloma is one of the breast masses difficult to differentiate from breast bud, but sometimes the surgeon must perform excisional biopsy to define the pathology, to end the fearful days and months of the children and parents with bloody or yellowish discharge and local pain(5,9).If indicated intraoperative identification of the papilloma, must be followed by the excision of the involved duct and a small rim of surrounding breast tissue(1).Follow up with careful physical examination is essential; when the mass is persistent, enlarging or symptomatic, surgical excision is advised(4). Intraductal papillary tumors which originate in the large and peripheral ducts are seen generally with no evidence of palpable mass but a bloody or yellowish green nipple discharge making a distinction between benign and malign lesions. After the determination of the origin, the excision of the papilloma should be performed. The recurrence rate of intraductal papilloma has been reported to be 65 % in three years time after treatment (10). This should be kept on minds during the follow up period.

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