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EFFECT OF VERIFICATION BIAS ON SENSITIVITY AND SPECIFICITY OF DIAGNOSTIC TESTS

Yasemin Genç* ✣ Ersöz Tüccar*

SUMMARY

To evaluate the accuracy of a diagnostic test, we need to have an unbiased estimate of the test's accuracy and to provide this, the disease status for each patient have to be determined independent of the patient's test result. The procedure that establishes the patient's disease status is referred to as a gold standard. In practice, however, selection of patients for gold standard is often influenced strongly by the test results. When it occurs, accuracy of the tests such as sensitivity and specificity may be biased. This type of bias is called "verification bias".

In this study, we aimed to show the effect of the verification bias on sensitivity and specificity of the thyroid palpation. Thyroid palpation is commonly used diagnostic test for determining thyroid nodules. Estimation of sensitivity and specificity of the thyroid palpation were obtained respectively through Begg and Greenes's correction method and the conventional method.

Parallel to the other studies, this study indicates that ignoring the use of the selected subjects, the sensitivity is inflated and specificity is deflated.

Key Words: Begg and Greenes Correction Method, Sensitivity, Specificity, Verification Bias

ÖZET

Seçilmiş Deneklerin Kullanılmasının Tanı Testlerinin Duyarlılığı ve Seçiciliği Üzerine Etkisi

Bir tanı testini değerlendirirken testin doğruluk ölçütlerinin yansız kestirimine ihtiyacımız vardır. Bunu sağlamak için deneklerin hastalık durumu tanı testi sonuçlarından bağımsız olarak elde edilmelidir. Deneklerin hastalık durumları "altın standart" testlerle belirlenebilir. Fakat pratikte altın standart test uygulanacakların seçimi tanı testi sonuçlarından oldukça etkilenir. Böyle bir durumda duyarlılık ve seçicilik gibi doğruluk ölçütleri yanlı kestirilir. Bu tip bir yan tutma "seçilmiş deneklerin kullanılmasından kaynaklanan yan" olarak adlandırılır.

Bu çalışmada amaç seçilmiş deneklerin kullanılmasının "Troid Palpasyonu"nun duyarlılığı ve seçiciliği üzerine etkisini göstermektir. Troid palpasyonu, tiroid nodüllerinin saptanmasında kullanılan bir tanı testidir. Troid palpasyon'unun duyarlılığı ve seçiciliği sırasıyla Begg ve Greenes'in düzeltme yöntemi ve geleneksel yöntem ile elde edilmiştir.

Diğer çalışmalara paralel olarak bizim çalışmamız da seçilmiş denekler kullanıldığında duyarlılığın gerçekte olduğundan daha yüksek seçiciliğin daha düşük elde edildiğini göstermiştir.

***Anahtar Kelimeler:** Begg ve Greenes Düzeltme Yöntemi, Duyarlılık, Seçicilik, Seçilmiş Deneklerin Kullanılmasından Kaynaklanan Yan*

Parallel to the technologic advances, new diagnostic tests supposed to be better are advised. To put in routine use these tests, accuracy such as sensitivity, specificity, area under ROC curve must be obtained without any error. Therefore to evaluate the accuracy of a diagnostic test, we need to have an unbiased estimation. To obtain an unbiased estimator for the test's accuracy, the disease status for each patient have to be determined independent of the patient's test result. The procedure that establishes the patient's disease status is referred to as a gold standard. The gold standard may be based on surgery, biopsy, angiography or clinical assessments. In clinical practice, however, selection of patients for gold standard is often influenced strongly by the test results. For example if the gold standard is based on invasive

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surgery, then patients with positive test results will tend to receive the gold standard than patients with negative test results. Although it may be more ethical and cost-effective in clinical researches, the estimates of accuracy can be biased in a study with such a design. Firstly, this type of bias was called "work-up bias" by Ransohoff and Feinstein (1). Later, instead of "work up bias" term, "verification bias" has been used mostly (2-4).

More often, in addition to test result, sign and symptoms relating to the disease in question can also influence the selection. For example, a patient undergoing mammography for breast cancer with an equivocal test result may be more likely to receive a subsequent biopsy if a mass is thought to be palpable on physical examination.

To illustrate how verification bias may arise and to explore its potential effects, we consider a hypothetical example of estimating the sensitivity of a Fine Needle Aspiration Biopsy (FNAB) in diagnosis of liver cancer. Surgery is used as the gold standard for liver cancer. Assume the actual sensitivity of the FNAB is 70% . Thus, 30% of all diseased patients will have false-negative test results. We sample 100 patients who all have liver cancer (all have gold standard). All patients are tested with FNAB and we obtain 70 respond positively and 30 respond negatively. Since surgery is an invasive procedure, 80% of patients with positive test result and 10% of patients with negative test result were verified for surgery. Thus, among 70 patients who tested positive, 56 have surgery and among 30 who tested negative, only 3 have surgery. Estimation using only verified patients would lead to the incorrect conclusion that the sensitivity of the FNAB is 95% (56/59), a gross overestimation of the true sensitivity.

Without application of a gold standard to all subjects, the only way of providing an unbiased estimation of diagnostic measures is to use correction methods in calculations. The most common correction method for the unbiased estimation of sensitivity and specificity is the one proposed by Begg and Greenes (2).

In this study, we aimed to show the effect of the verification bias on the sensitivity and the specificity of the thyroid palpation. Estimation of sensitivity and the specificity of the thyroid palpation were obtained respectively through the use of correction method proposed by Begg and Greenes and conventional methods without taking in consideration the selected subjects.

Methods

Begg and Greenes correction method

Define the random variables T, D, V and X for an individual case as follows:

T, value of diagnostic test result;

T=1 Positive test result

T=0 Negative test result

D, disease status;

D=1 Diseased

D=0 Not diseased

V, selection variable;

V= 1 case selected for gold standard

V=0 case not selected for gold standard

X, concomitant information (vector of sign and symptoms)

To infer disease information about the non-verified cases, the assumption of independence or conditional independence between V and D is necessary. The rationale for the assumption of conditional independence is that selection may only be influenced by "visible" factors, i.e. the test result (T) and signs and symptoms (X). Although the disease process affects both T and X, it only affects selection through its influence on T and X. Consequently, D and V are conditionally independent.

Under this assumption;

$$p(D/T)=p(D/T, V=1) \quad (1)$$

The primary objective is to estimate sensitivity (Sens) and specificity (Spe). Using Bayes's theorem and substituting equation (1);

$$\text{Sens} = (T = 1 / D = 1) = \frac{p(T = 1)p(D = 1 / T = 1, V = 1)}{\sum_{T=0}^{1} p(T)p(D / T, V = 1)}$$

$$\text{Spe} = p(T = 0 / D = 0) = \frac{p(T = 0)p(D = 0 / T = 0, V = 1)}{\sum_{T=0}^{1} p(T)p(D / T, V = 1)} \quad (2)$$

The observed data with verification bias may be displayed as in Table 1.

Table 1. Cross-classification of test results by disease status and verification status

		Test result	
Verification status	Disease Status	T=1	T=0
V=1	D=1	s_1	s_2
	D=0	r_1	r_2
V=0		u_1	u_2
	Total	n_1	n_2

Using observed data, sensitivity and specificity are defined as,

$$\text{Sens} = (T = 1 / D = 1) = \frac{\frac{n_1 s_1}{s_1 + r_1}}{\frac{n_1 s_1}{s_1 + r_1} + \frac{n_2 s_2}{s_2 + r_2}}$$

$$\text{Spe} = p(T = 0 / D = 0) = \frac{\frac{n_2 s_2}{s_2 + r_2}}{\frac{n_1 s_1}{s_1 + r_1} + \frac{n_2 s_2}{s_2 + r_2}} \quad (3)$$

Begg and Greenes (2) also gave the estimators of approximate variances of their proposed estimators for sensitivity and specificity. Their proposed estimators are defined as follows:

$$\text{var}[\text{Sens}] = (\text{Sens}(1 - \text{Sens}))^2 \left(\frac{n}{n_1 n_2} + \frac{r_1}{s_1(s_1 + r_1)} + \frac{r_2}{s_2(s_2 + r_2)} \right)$$

$$\text{var}[\text{Spe}] = (\text{Spe}(1 - \text{Spe}))^2 \left(\frac{n}{n_1 n_2} + \frac{s_1}{r_1(s_1 + r_1)} + \frac{s_2}{r_2(s_2 + r_2)} \right) \quad (4)$$

In practice, it is more probable that selection will also depend on the concomitant information X. Therefore we may assume that;

$$P(D/R, X) = P(D/R, X, V=1) \quad (5)$$

Therefore,

$$\text{Sens} = p(T = 1 / D = 1) = \frac{\sum_X p(T = 1, X)p(D = 1 / T = 1, X, V = 1)}{\sum_{T=0}^{1} \sum_X p(T, X)p(D / T, X, V = 1)}$$

$$\text{Spe} = p(T = 0 / D = 0) = \frac{\sum_X p(T = 0, X)p(D = 0 / T = 0, X, V = 1)}{\sum_{T=0}^{1} \sum_X p(T, X)p(D / T, X, V = 1)} \quad (6)$$

An Example

The data obtained in our study were gathered from Ankara University, Medical Faculty, Department of Endocrinology and Metabolic Diseases in 1999. Data from patients applied to Endocrinology out patient clinic was transferred to software called "Endoline". Endoline, which was developed specifically for the use of Department of Endocrinology and Metabolic Diseases has now been used by five hospitals in Turkey. It involves information about complaint, physical examination, diagnosis, treatment and surgery and enable to statistical analysis.

Palpation is commonly used diagnostic test for determining thyroid nodules. Because of its ease and does not necessitate the use of any drug or device it is preferred especially for prevalence studies. Another method for determining thyroid nodules is Ultrasonography (USG). It is used as a gold standard in studies since it is sensitive in determining nodules as small as 2-3 mm.

Although USG is a non-hazardous, non-invasive and cost-effective method, palpation is preferred rather than USG in prevalence studies. In our study, we aimed to estimate sensitivity and specificity of palpation in determining thyroid nodules. As it is seen in other studies, our data mostly consists of patients who have undergone only thyroid palpation, without confirmation with USG. It was noticed that, USG was applied to 1.94% of patients with thyroid nodules and 0.52% of patients without thyroid nodules which can lead to verification bias in this kind of studies. Therefore to have an unbiased estimates, retrospective correction method must be used. In our example, unbiased estimates of sensitivity and specificity were obtained through the use of correction method proposed by Begg and Greenes. To assess the effect of verification bias on the estimates, conventional method was also used. There wasn't any concomitant information in our example.

Begg and Greenes correction method

Sensitivity and specificity of thyroid palpation was obtained by Begg and Greenes correction method as below.

There were 9531 patients who participated in the study. Of the 5358 patients who had palpable nodules, 104 were referred to undergo disease verification procedures. Of 4173 patients without palpable nodules, only 22 were referred to undergo disease verification procedure.

Data are presented in Table 2.

Table 2. Cross-classification of Thyroid Palpation results by USG results and verification status according to observed data

		Thyroid Palpation	
Verification status	USG	Palpable nodules present	Palpable nodules absent
V=1	Nodules present	62	6
	Nodules absent	42	16
V=0		5254	4151
	Total	5358	4173

Using Equation (3) and (4) sensitivity, specificity and their variances were obtained by Begg and Greenes method as follows.

$$\text{Sens} = (T=1/D=1) = \frac{\frac{5358x62}{62+42}}{\frac{5358x62}{62+42}+\frac{4173x6}{6+16}} = 0,7373$$

$$\text{Spe} = p(T=0/D=0) = \frac{\frac{4173x16}{6+16}}{\frac{4173x16}{6+16}+\frac{5358x42}{62+42}} = 0,5838$$

$$\text{var[Sens]} = (0,7373(1-0,7373))^2 \; x\left(\frac{9531}{5358x4173}+\frac{42}{62(62+42)}+\frac{16}{6(6+16)}\right)$$

$$= 0,0018$$

$$\text{var[Spe]} = (0,5838(1-0,5838))^2 \; x\left(\frac{9531}{5358x4173}+\frac{62}{42(62+42)}+\frac{6}{16(6+16)}\right)$$

$$= 0,0019$$

Conventional method

As it's mentioned above, in many studies, accuracy is obtained by conventional method without taking in consideration the selected subjects. In part of our study, to assess effect of verification bias on the sensitivity, specificity and their variances, conventional method was also used.

Data related to 126 patients are presented in Table 3.

Table 3. Cross-classification of Thyroid Palpation results by USG results according to observed data

	Thyroid Palpation	
USG	Palpable nodules present	Palpable nodules absent
Nodules present	62	6
Nodules absent	42	16
Total	104	22

$$Sens = (T = 1 / D = 1) = \frac{s_1}{s_1 + s_2} = \frac{62}{62 + 6} = 0,9118$$

$$Spe = p(T = 0 / D = 0) = \frac{r_1}{r_1 + r_2} = \frac{16}{42 + 16} = 0,2759$$

$$Var[Sens] = (T = 1 / D = 1) = \frac{Sens(1 - Sens)}{n_{D=1}}$$

$$= \frac{0,9118(1 - 0,9118)}{68} = 0,0012$$

$$Var[Spe] = p(T = 0 / D = 0) = \frac{Spe(1 - Spe)}{n_{D=0}}$$

$$= \frac{0,2759(1 - 0,2759)}{58} = 0,0034$$

Result

In our study, estimation of sensitivity and specificity of the palpation method used in the identification of trioid nodules was done through the use of the correction method proposed by Begg and Greenes and conventional method. When the method developed by Begg and Greenes was used, the sensitivity was estimated as 0,7373 and its variance as 0,0048. When conventional method was employed, sensitivity was found as 0,9118 and its variance as 0,0012. With the correction method, the specificity was found 0,5838 and its variance as 0,0019. When the conventional method was employed, the specificity was found 0,2759 with the variance value of 0,0034.

Parallel to the other studies (4,5), this study indicates that ignoring the use of the selected subjects, the sensitivity is inflated and specificity is deflated.

Although verification bias can distort .the estimated accuracy of a diagnostic test, many published studied on the accuracy of diagnostic tests fail to recognize verification bias. For example, Greenes and Begg (5) reviewed 145 studies published between 1976 and 1980 and found that at least 26% of the articles had verification bias, but failed to recognize it; Bates et al. (6) reviewed 54 pediatric studies and found more than one third had verification bias; and Philbric et al. (7) reviewed 33 studies on the accuracy of exercise tests for coronary disease and found that 31 might have had verification bias.

Since it is often unethical or impractical to verify all study patients, retrospective adjustments are needed to provide correct inferences about the accuracy of tests.

Conclusion

In sum, it is important to know that using proper diagnostic tests, patient's life can be saved and that medical costs can be reduced with a larger perspective. Therefore accuracy of diagnostic tests should be developed without any error.

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MICROORGANISMS ISOLATED FROM CATHETER TIP CULTURES: İBN-İ SİNA HOSPITAL 2002

Özay Arıkan Akan*

SUMMARY

Semiquantitative and quantitative cultures of 282 catheter tips from patients hospitalized in different units in Ibni Sina Hospital showed significant growth in 57.1% and in 47.1% respectively by the two techniques. Highest positivity was found in catheters sent from surgery unit (85%) followed by reanimation unit (59.7%). Among the positive cultures coagulase negative staphylococci (60/161), S.aureus (35/161) and A.baumannii (28/161) were the most common isolates. Polimicrobial growth was 8%. High rate of culture positivity shows us the need of prospective detailed studies with clinical information of the patients and catheter types included in the study. Dialog should be established between Surgery unit and Central Laboratory since the number of catheters sent from surgery unit was very low (n:20) during one year period.

Key Words: *Intravascular Catheter, Semiquantitative Tip Culture, Quantitative Tip Culture, Colonization.*

ÖZET

Kateter Ucu Kültürlerinde İzole Edilen Mikroorganizmalar: İbn-i Sina Hastanesi 2002

Ankara Tıp Fakültesi İbni Sina hastanesi çeşitli bölümlerinde yatan hastalardan alınan 282 kateter ucu semikantitatif ve kantitatif kültürlerle değerlendirilmiştir. Bu iki teknikle sırayısıyla %57.1 ve %47.1 üreme saptanmıştır. En fazla üreme Genel Cerrahi kliniğinden (%85) gelen kateterlerde olmuş, bunu reanimasyon ünitesi (%59.7) izlemiştir. Pozitif kültürlerde koagülaz negatif stafilokok (60/161), S. aureus (35/161) ve A. baumanii (28/161) en sık rastlanan etkenler olmuştur. Yüzde 8 oranda polimikrobial üreme görülmüştür. Kültürde üreme oranlarının bu kadar yüksek olması hastaların klinik bilgilerini ve kateter tiplerini içine alan ayrıntılı prospektif çalışmalara ihtiyaç olduğunu göstermektedir. Genel Cerrahi kliniğinden gelen kateter miktarının düşük olması (n:20) Merkez Laboratuvarı ile Genel Cerrahi kliniğinin daha yakın ilişkide olması gerekliliğini göstermektedir.

Anahtar Kelimeler: *İntravasküler Kateter, Semikantitatif Kateter Kültürü, Kantitatif Kateter Kültürü, Kolonizasyon.*

Localised or systemic infections are frequent complications associated with extensive use of foreign devices in modern medicine. Intravascular catheters are one of the most widely used devices in multidisciplinary medical practice. Infections of these catheters not only cause high expences due to loss of the catheters but may cause bacteremia and sepsis with high mortality as well. Many efforts have been applied both for prevention and management of such infections. The agent responsible from colonisation and infection is important for the therapeutic approach for the choice of antibiotic therapy and decision of the catheter removal (1,2,3). Every medical center has its own patient and medical care groups and medical behaviour that will affect microbial flora and it should be closely monitored by the microbiology laboratory to decide on the preventive actions and empirical antimicrobial choices.

The aim of this study is to show the microbial spectrum and rate of colonisation/infection in different intravascular catheters used in different units in İbni Sina Hospital.

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Method

Tips of the intravenous catheters obtained from hospitalized patients sent to the Central Diagnostic Laboratory of İbni Sina Hospital were cultured using semiquantitative tip culture method followed by quantitative technique. Semiquantitative tip culture method is the classical roll plate method described by Maki. For quantitative technique 5-7 cm catheter tip is put in 1 ml of brain heart infusion broth and vortexed for 10 minutes. 100 mcg of broth is poured on to blood and chocolate agar plates. After 24 and 48 hours all of the plates were evaluated for growth of microorganisms. >15 cfu and >1000 cfu/ml respectively were considered as positive according to the protocols (4,5).

Identification of bacteria are performed by classical microbiological techniques and mini API (bioMerieux) system where necessary (6).

Results

During 1.1.2002 and 31.12.2002 a total of 282 catheter tips sent to the Central Laboratory from different wards were evaluated. 121 (42.9%) of them were sterile. The results were compatible in 133 catheters but 28 (Staphylococcus spp 17, gram negative bacilli 7, streptococcus spp 1, Candida albicans 1, diptheroids 2) were found positive only by semiquantitative technique. The highest isolation rate was found in surgery unit (85%). The services and the culture positivity results are shown in Table 1. Single microorganism was observed in all but 13 (8%). Types of the microorganisms observed in mixed growth is shown in Table 2. Coagulase negative staphylococci, S.aureus and A.baumanni were the most common isolates respectively baumannii (Table 3). Seventy percent of gram negative bacilli were mostly seen in the reanimation unit. Among the 5

Table 1: Distribution and positivity among the catheters due to the wards

Unit	No of Catheters	Positive cultures	Colonisation/infection rate
Reanimation	139	83	59.7
Internal medicine*	123	61	49.5
Surgery	20	17	85
Total	282	161	57.1

*62 catheters are from the haematology unit .

Table 2: Mixed growth of microorganisms and their origin

	Unit	Bacteria 1	Bacteria 2
1	Reanimation	S.aureus	A.baumannii
2	Reanimation	P.aeruginosa	CNS
3	Reanimation	K.pneumoniae	CNS(S.epidermidis)
4	Reanimation	K.pneumoniae	S.aureus
5	Reanimation	S.aureus	Enterobacter cloacae
6	Reanimation	Enterobacter cloacae	P.aeruginosa
7	Reanimation	A.baumannii	S.maltophilia
8	Reanimation	A.baumannii	P.aeruginosa
9	Reanimation	A.baumannii	E.coli
0	Reanimation	A.baumannii	Citrobacter freundii
11	Gastroenterology	S.aureus	CNS (S.epidermidis)
12	General Surgery	S.aureus	Gram neg. bacilli
13	Haematology	Candida dublinensis	A.baumannii

Table 3. Microorganisms isolated (semiquantitative technique)

Microorganisms	n	% of total isolates
Gram positive cocci	104	59.7
Staphylococcus aureus	35	
Coagulase negative staphylococci	60	
Micrococcus luteus	3	
Enterococcus spp	5	
Streptococcus spp	1	
Gram positive bacilli	5	2.9
Corynebacterium spp	1	
Diphteroids	4	
Gram negative (fermentative)	18	10.3
Escherichia coli	7	
Klebsiella pneumoniae	4	
Klebsiella oxytoca	1	
Enterobacter spp.	5	
Citrobacter freundii	1	
Gram negative (non –fermentative)	43	24.7
Acinetobacter baumannii	28	
Stenotrophomonas maltophilia	3	
Pseudomonas aeruginosa	8	
Nonfermentative gram negative bacilli	4	
Candida spp	4	2.3
Candida albicans	1	
Non albicans	3	
Total		174

Candida species 2 were C.albicans, one was C.dublinensis and 2 were nontypable.

Discussion

The high incidence of bacteriemia by extensive use of intravascular devices caused special interest in the microbiology and pathogenesis of catheter related infections. Once catheter infection is decided the therapeutic approach will be affected by the severity and the type of infection, status of the patient and the necessity of the catheter and the type of the etiologic agent (7,8,9). The spectrum of microorganisms should be known to decide about the route of infection and to take preventive measures and to decide empirical antibioitic therapy. Vascular catheter infections can develop for many reasons but they must begin with catheter colonisation by microorganisms through either one or both of two routes; colonisation of the outside catheter by either skin microorganisms or hematogenous seeding from a distant site, colonisation of inside of the catheter by the introduction of microorganisms through catheter hub or contamination of infusion fluid (10,11). Early catheter infections are caused primarily by skin microorganisms, and late infections by catheter lumen or hub contamination. Depending on studies the two most common microorganisms involved in catheter colonisation and/or infection are S.epidermidis and S.aureus (12,13). S.epidermidis has the ability to survive in the presence of a foreign body. Adhesin and pili like structures were shown to play role in adherence. Slime production is another virulence factor in S.epidermidis. Demonstration of S.aureus with enhanced virulence in the presence of a foreign body has been shown. It has the ability to adhere surface proteins and form glycocalyx which may help them evade phagocytosis (14,15). In our study CNS and S.aureus were the two most common isolates. Gram negative bacilli and particularly A.baumannii was the third common isolate in our study. For years intravascular devices as source of nosocomial gram negative bacteremia has been undefined. Though less often implicated than gram positive microorganisms, gram negative bacilli particularly the enterobacteriaceae members, P.aeruginosa and Acinetobacter spp. account for up to one-third of infections associated with most intravascular devices.(16,17) Mortality of bacteremia due to Pseudomonas aeruginosa is reported to be high however it is believed to be lower in catheter related bloodstream infections (18) Unlike gram positives, pathogenesis of gram negative bacteria in catheter infections has been rarely investigated. Particularly the nonfermentatives live well in moist environments and live in contaminated infusions. P.aeruginosa and Acinetobacter spp. may have spesific adherence properties and

biofilm formation. Our high isolation rate is probably due to our high number of catheter tips sent from the reanimation unit where A.baumannii is a frequent colonizer. Gram negatives may colonize the intravascular catheters in the same manner as common gram positives which are present in human skin (19). In our report Stenotrophomonas maltophilia (one from reanimation unit and 2 from nephrology unit) is remarkable. It may alarm us for the introduction of a new nonfermentative gram negative in catheter related infections. The overall incidence of Candida infections due to intavascular devices has been increased, but our isolation rate is less than that of the similar studies. In the literature, colonization rates between 5%-27% are mentioned (20,21).

Our data showed significant growth in more than 50% of catheters included in the study. With the clinical informations of the patients, catheter related infection and septicemia rates in our hospital must be established. During one year period only 20 tip cultures from surgery units is questionable. Importance of clinical microbiology laboratory in the diagnosis of catheter related infections should be emphasized to the surgeons.

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NEUROBRUCELLOSIS AS AN EXCEPTIONAL CAUSE OF TRANSIENT ISCHEMIC ATTACKS

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SUMMARY

Incidence of neurologic complications in systemic brucellosis has been reported as 2-10%. Neurobrucellosis (NB) can mimic many central and peripheral nervous system disorders including transient ischemic attacks (TIA), and ischemic or hemorrhagic stroke.

We report a series of four cases presented with TIA or ischemic stroke as the predominant manifestation of NB. Three of the patients were 20-28 years of age, and one patient was 53 years old. They did not possess any stroke risk factors except for smoking. They all used to consume pasteurized milk or its products. Two patients had systemic brucellosis in the past and received antibiotic treatment. All of the patients had systemic symptoms such as headache, fatigue, anorexia, nausea and vomiting, weight loss or lumbar pain, but no systemic signs of brucellosis accompanying ischemic cerebral symptoms. The second most frequent neurological sign was sensorineural hearing loss. Other causes of TIA including cardiac embolism, hypercoagulability, vascular malformations, systemic vasculitis, and infective endocarditis were excluded. NB was diagnosed with serological tests or cultures for Brucella in CSF. All patients were treated with trimethoprim-sulfamethoxazole, doxycycline and rifampicin for at least six months. None of them had any further TIA after the initiation of the treatment

NB should always be sought in young patients with TIA or ischemic stroke, especially if they have no risk factors for stroke and live in an endemic area for brucellosis, even if they do not have other systemic signs of brucellosis.

Key Words: *Transient Ischemic Attack, Ischemic Stroke, Brucellosis*

ÖZET

Nadir Bir Geçici İskemik Atak Nedeni: Nörobrusellozis

Sistemik brusellozda nörolojik komplikasyonların insidansı %2-10 olarak bildirilmektedir. Nörobrusellozis (NB), geçici iskemik atak (TİA), iskemik veya hemorajik strok da dahil pek çok santral ve periferik sinir sistemi hastalığını taklit edebilir.

NB'un önde gelen belirtisi olarak TİA veya iskemik stroklu 4 hastalık bir seri bildiriyoruz. Üç hastanın yaşı 20-28 arasında idi, birinin yaşı 53 idi. Sigara içme dışında herhangi bir risk faktörleri yoktu. Hepsi de pastörize süt ve süt ürünleri tüketmekteydi. 2 hastanın özgeçmişinde sistemik bruselloz vardı ve tedavi almışlardı. Hepsinde de baş ağrısı, halsizlik, iştahsızlık, bulantı, kusma, kilo kaybı, bel ağrısı gibi sistemik semptomlar vardı ama iskemik serebral semptomlar dışında herhangi bir sistemik bruselloz bulguları yoktu. İkinci sıklıktaki nörolojik bulgu sensorinöral işitme kaybıydı. Kardiak embolizm, hiperkoagülabilite, vasküler malformasyonlar, sistemik vaskülit ve enfektif endokardit dahil diğer TİA nedenleri ekarte edildi. NB tanısı BOS'ta Brucella'ya spesifik serolojik testler veya kültür ile kondu. Tüm hastalar trimetoprim-sulfametoksazol, doksisiklin ve rifampisinle en az 6 ay boyunca tedavi edildi. Tedavi başlandıktan sonra hiç birinde TİA tekrarı olmadı.

TİA veya iskemik stroku olan genç hastalarda, özellikle de strok için risk faktörleri yoksa ve brusellozun sistemik olduğu bir bölgede yaşıyorlarsa, NB araştırılmalıdır.

Anahtar Kelimeler: *Geçici İskemik Atak, İskemik Strok, Brusellozis*

Brucellosis is still a common health problem in some Middle Eastern and Mediterranean countries, although it has been almost eradicated in many developed countries. Nervous system involvement occurs approximately in 2-10% of the patients infected with brucella (1-4).

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Neurobrucellosis (NB) may develop at any stage in the evolution of the disease and may involve several areas of the central and peripheral nervous system. Therefore, NB has widely variable manifestations, including meningoencephalitis, myelitis, radiculitis, neuritis, spinal cord compression and demyelinative or vascular diseases of the central nervous system (CNS), or any combination of these disorders (1-9). The majority of patients exhibit symptoms that fit into more than one category.

The most typical presentation of CNS involvement in brucellosis is chronic meningoencephalitis with mononuclear pleocytosis, low glucose and increased protein concentrations in the cerebrospinal fluid (CSF) (1). Uncommon clinical presentations of NB such as migraine, parkinsonism, optic neuritis, chronic intracranial hypertension, and epilepsy were described (8,10-15). Brucellar meningitis may also behave as an exclusively neurologic disease, mimicking vascular accidents or neurological diseases that are frequently paroxysmal and recurrent (16). Here we report a series comprising four cases with brucellar meningitis as an exceptional cause of transient ischemic attacks (TIA) and ischemic stroke.

Case Reports

Case 1: A 24-year-old woman was admitted with repeated episodes of right hemiparesis, hypoesthesia and dysphasia that were lasting at most an hour. She had experienced eight similar episodes in the last month. The patient was also complaining of having lumbar pain, headache, nausea and vomiting, anorexia and weight loss for the last six months. Her lumbar pain had been attributed to sacroiliitis previously. Physical examination was normal. The neurological examination during the last episode revealed motor dysphasia, right hemiparesis, and hypoesthesia, abolished abdominal skin reflex and plantar reflex on the right side. Between these episodes, the neurological examination was completely normal.

Laboratory examinations revealed mildly increased liver enzymes and erythrocyte sedimentation rate (ESR) of 24 mm/hour. Blood counts, prothrombin time (PTT), activated partial thromboplastin time (aPTT), fibrinogen, antithrombin III (AT III), protein C, protein S, activated protein C resistance (aPCR), and antiphospholipid antibodies were within the normal ranges. Immunologic markers including immunoglobulins, C3, C4, crioglobulin, and antinuclear antibodies were negative. No abnormal finding was observed on the plain x-ray of the chest. Cranial computerized tomography (CCT) was normal, but magnetic resonance imaging (MRI) showed a small linear lesion with increased intensity on T2 weighted images (WI) and decreased intensity on T1 WI localized in the posterior insular cortex. Magnetic resonance angiography (MRA) and four-vessel digital substraction angiography (DSA) of the brain were unremarkable. Transthoracic (TTE) and transeosophageal echocardiography (TEE) showed no abnormality to be the cause of cardioembolism.

Since she used to consume fresh cheese made of cow's milk and has sacroiliitis, brucellosis was considered in the differential diagnosis. Brucella agglutination and Coombs' tests in blood were both positive in a titer of 1/160. Brucella Rose-Bengal and Ig M (2-mercaptoethanol) were also positive in blood. Cerebrospinal fluid (CSF) appeared clear with an opening pressure of 45cm water. CSF results were shown on the Table 1&2. CSF cultures yielded Brucella melitensis and antibiogram showed susceptibility to rifampicin and doxycycline.

Brucellar meningitis with TIA was diagnosed and treatment with trimethoprim 160 mg/sulfamethoxazole 800mg (TMP-SMZ) three times a day, doxycycline 200 mg/day and rifampicin 900 mg/day was started. In the forth month of the therapy, CSF analysis was repeated. There was no abnormality in CSF examinations except for the positive Coombs' tests. The patient remained free of TIA since the beginning of the treatment.

Table 1: The results of cerebrospinal fluid (CSF) examinations

	CASE 1	CASE 2	CASE 3	CASE 4
Leukocyte (N:<10/mm3)	**120**	**48**	**50**	**52**
Total protein (15-45 mg/dl)	30	**181**	**127**	**77**
Albumin (15-40 mg/dl)	15	**86**	**84**	**43**
CSF/blood glucose (mg/dl)	**20/106**	**13/91**	**3/72**	**26/75**
Ig G (3.3-6.1 mg/dl)	4.2	**16.2**	**13.9**	**15**
Ig A (0.00-0.60 mg/dl)	0.5	**2.1**	**3.64**	0.4
Ig M (0-1.3 mg/dl)	0.8	1.0	0.6	1.2
Ig G index (0.2-0.50)	0.45	**0.60**	**0.64**	**2.15**
Oligoclonal band	–	+	NE	+

NE: not evaluated, pathologic results are shown in **bold**

Table 2: The results of serological tests and blood culture for brucella in blood and cerebrospinal fluid (CSF) prior to the treatment

	CASE 1	CASE 2	CASE 3	CASE 4
B. agglutination test (blood)	1/40	1/40	NE	**1/80**
B. agglutination test (CSF)	–	**1/20**	**1/40**	**1/20**
Coombs' test (CSF)	–	**1/80**	**1/160**	**1/160**
Rose-Bengal test (CSF)	–	–	+	–
Ig M (2-ME) (CSF)	–	–	+	–
CSF culture	+	–	–	+

NE: not evaluated, pathologic results are shown in bold.

Case 2: A 20-year-old man presented with repeated transient episodes of right hemiplegia and motor aphasia. He had had three similar episodes in the last six months that relieved in a few hours. He was examined by a psychiatrist therefore and treated with antidepressant agents and electroconvulsive therapy. He has been also complaining of having fatigue, nausea, lumbar pain, and a hearing loss in both ears for one year. His physical examination was normal and neurological examination revealed sensorineural hearing loss in the right ear. Audiogram was consistent with bilateral sensorineural hearing loss predominantly in the right ear.

Blood chemistry, blood count, coagulation profile, and hematologic tests for hypercoagulability were normal, and immunologic markers were negative. ESR was 41 mm/hour. CCT showed a focal hypodense lesion with 8mm diameter in the right temporal lobe next to the sylvian fissure. MRI of brain revealed a lesion with increased intensity on T2 WI in the right temporal lobe. Duplex ultrasound of the carotid arteries, TTE and TEE were unremarkable. Brucella agglutination and complement fixation tests in blood were positive in a titer of 1/40 and 1/20, respectively. CSF results were compatible with NB (Table 1&2). Lyme screen, polymerase chain reaction (PCR) for Mycobacterium

tuberculosis and CSF cultures for brucella and bacteria were negative. The patient was placed on TMP-SMZ three times a day, doxycycline 200 mg/day and rifampicin 900 mg/day.

CSF examination repeated in the forth month of the therapy was not significantly different from the one performed prior to the treatment. However, oligoclonal band was not observed at this admission. Brucella agglutination, Coombs' and Rose-Bengal tests in CSF remained positive. His sensorineural hearing loss was still remaining in the second year of the treatment, but transient episodes of right hemiparesis and aphasia disappeared after a short time of the treatment.

Case 3: A 53-year-old man was admitted with multiple transient episodes of hemiparesis, hypoesthesia and speech disorder improving in an hour and progressive hearing loss in both ears for six months. The last attack that occurred four days before his admission was characterized with nausea-vomiting, tetraparesis and speech arrest, and disappeared in a few hours. He has been complaining of having continuous headache that was not completely responsive to analgesic drugs. He was diagnosed to have brucellosis two years ago and treated with doxycycline 200 mg/day and rifampicin 600 mg/day for three months. He was consulted in the Ear-Nose-Throat Clinics for several times but the progressive hearing loss in his both ears could not be explained. He had no vascular risk factors except for smoking. He was using aspirin 300 mg/day regularly since his first transient ischemic attack.

His physical examination was normal and the neurological examination between the attacks revealed bilateral sensorineural hearing loss and Hoffmann and palmomental reflexes bilaterally. Audiogram showed intermediate sensorineural loss bilaterally. Blood chemistry, blood counts, urine analysis, chest radiography and electrocardiography were normal. ESR was 4 mm/hour. Coagulation profile and all hematologic tests for hypercoagulability were normal. TTE, TEE, duplex ultrasound of the carotid and vertebral arteries, and cerebral DSA were unremarkable. CSF analysis was showed on Table 1&2. Lyme screen, PCR for Mycobacterium tuberculosis and CSF cultures for brucella and bacteria were negative. MRI of brain showed bilateral gadolinium enhancement of trigeminal nerves in cisternal segment, and facial and vestibulocochlear nerves in cavernous segment. Besides, bilateral subcortical lesions in periventricular white matter with increased intensity on T2 WI were observed.

Transient ischemic attack due to brucellosis was diagnosed, and the treatment of TMP-SMZ three times a day, doxycycline 200 mg/day and rifampicin 900 mg/day was started. In the second week of the therapy, rifampicin was discontinued due to resistant nausea-vomiting, hiccup and elevation of hepatic enzymes. Other two drugs were also stopped a few days later, since his complaints did not relieve and hepatic and renal function tests impaired gradually. After the improvement of blood chemistry and the relief of his complaints, TMP-SMZ was restarted. Blood chemistry was evaluated weekly and doxycycline and rifampicin were also added to the treatment. The patient did not describe any new symptoms and TIA during the treatment period of one year.

Case 4: A 28-year-old man was admitted with dysarthria, left hemiparesis and hypoesthesia. The day before this event he experienced multiple attacks of weakness and numbness in the left arm that recovered in five minutes. The diagnosis of brucellosis was made one year ago and antibiotic treatment was started that he did not use regularly. He has had pain in multiple joints for one year, but no vascular risk factors in history. Blood chemistry, blood counts, coagulation profile, and hematologic tests for hypercoagulability were within normal limits, and immunologic markers were negative. MRI of brain showed a frontoparietotemporal infarct with hemorrhagic transformation. Cerebral angiography showed severe stenosis of the right middle cerebral artery. Angioplasty and stenting of the right middle cerebral artery was performed in follow-up of this patient.

On fifteenth day of his admission, right facial paralysis and hearing loss in the right ear

developed abruptly. His physical examination was normal. In neurological examination, there were right peripheral facial paralysis and sensorineural hearing loss in the right ear in addition to his previous findings. CSF analysis was performed (Table 1&2). Blood and CSF cultures yielded Brucella melitensis. The treatment of TMP-SMZ three times a day, doxycycline 200 mg/day and rifampicin 900 mg/day were started. Six months after the initiation of the therapy, he had no additional neurological deficits and was free of TIA and recurrent stroke. CSF analysis revealed no abnormality except for Ig G index in the level of 2.25 and brucella agglutination test in a titer of 1/80.

Discussion

Brucellosis, although almost eradicated in many parts of the world, still remains widespread and endemic in the developing countries (1,2,16-18). Neurological involvement during the course of brucellosis occurs in about 2-10% of the cases (1-4). Clinical diagnosis of NB can be very difficult because of various presentations. Several clinical forms of brucellosis affecting the CNS have been reported. These include meningitis, meningoencephalitis, myelitis, myelopathy and demyelination or vascular diseases of CNS (1-9).

The endemic occurrence of brucellosis in this area, positive serology or CSF cultures for brucella, exclusion of other infectious agents and causes of ischemic cerebral symptoms, and good response to treatment with oral antibiotics supported the diagnosis of NB in our patients. Our patients presented with episodes of neurological deficits that were compatible with dysfunction of a certain vascular region and improved in a few hours. Therefore, we defined these episodes as "transient ischemic attacks". A similar clinical presentation was also reported by other authors and defined as "transient brief attacks" or "intermittent cerebral vascular insufficiency"(1,2,7,19-23). There is some evidence that some of these attacks can be attributed to subarachnoid hemorrhage secondary to ruptured mycotic aneurysm. Transient brief attacks followed by a ruptured basilar artery aneurysm in one patient and accompanied by xanthochromia in another were reported (21,22). A patient describing several attacks of numbness starting in the right foot extending to the right half of the body died of subarachnoid hemorrhage due to ruptured mycotic aneurysm of the basilar artery (7). No evidence of subarachnoid hemorrhage or vascular malformation was found in our patients. Case 4 had TIA resulting in ischemic stroke due to right middle cerebral artery infarct. Then he developed dysfunction of the cranial nerves 7 and 8.

The pathogenesis of TIA and ischemic stroke in brucellosis still remains uncertain. It has been proposed before, that TIA in brucellosis may be related either to infectious vasculitis or cerebral vasospasm or cardioembolism (1,2,19). Various degrees of vascular inflammation ranging from chronic to acute with the possibility of necrosis and aneurysmal formation have been described in CNS brucellosis (7). Carotid angiogram disclosed diffuse vascular spasm in the territory of the middle cerebral artery in a patient with several attacks of numbness starting in the fingers of the right hand extending to the right arm, shoulder and the right half of the face (23). As in ours, most of the patients with ischemic cerebral symptoms in the literature have normal cerebral angiograms (2). Al-Deeb has reported a man who presented with dysarthria and left hemiplegia of acute onset. CT showed a frontoparietal infarct, but cerebral DSA was normal (1). The authors proposed that normal appearance of cerebral vessels in DSA was consistent with vasculitis of deep penetrating arteries (1). We think that cardioembolism does not account for TIA in this series, since cardiac examination and both transthoracic and transoesophageal echocardiographies were normal in all patients.

As a manifestation of basal meningeal infection involvement of one or more cranial nerve has been noted in over one-half of cases (2). The vestibulo-cochlear nerve has been described as the most frequently involved cranial

nerve in NB. Its involvement is usually combined with other neurological dysfunctions (2,16,18,24). Although hearing loss is usually irreversible, further deterioration can be averted by appropriate treatment. Three cases in this series suffered hearing loss with a stable course but no relief after antibiotic treatment, while one patient (Case 4) had facial nerve involvement in addition.

NB may develop at the onset of the illness, during convalescence or months to years after recovery from the acute infection (5,18). Brucellosis was diagnosed in three of our patients previously, and they were treated with antibiotics for a certain period, however none of the patients had systemic manifestations of the disease, such as fever, hepatomegaly, splenomegaly, and lymphadenopathy in physical examination. TIA and ischemic stroke were the predominant manifestations of brucellosis in all patients. Only one of the patients reviewed by us had a focal extraneurologic involvement (sacroiliitis).

The final diagnosis of NB was made on the basis of the serological tests or culture for brucella in CSF. Other criteria supporting our diagnosis were: 1) systemic complaints of brucellosis, such as headache, malaise, weight loss, anorexia, lumbar pain and nausea-vomiting, 2) progressive bilateral sensorineural hearing loss without other known cause, 3) TIA not associated with other well-known risk factors of ischemic stroke, 4) lymphocytic pleocytosis in CSF with increased level of protein, and decreased level of glucose.

Low glucose values, lymphocytic pleocytosis and high protein content and Ig G values are usually found in CSF analysis of NB patients (2). All of our patients had low glucose levels and lymphocytic pleocytosis as an evidence of chronic meningeal inflammation. Three patients had increased protein and Ig G levels in CSF in addition to other abnormal findings. Tuberculosis may cause similar abnormalities in CSF but was excluded with PCR in these cases. In chronic NB increased Ig G index and/or oligoclonal banding pattern in CSF electrophoresis can be detected as in many other chronic inflammatory processes of the CNS (2,16,18). Normal levels of Ig M in serum and CSF were also indicating that infection has reached a chronic stage.

The serological study of both serum and CSF is essential for the diagnosis of NB. The most frequently used method for screening brucellosis is still the standard agglutination test. In active brucellosis high titres of Ig M antibodies can be detected by standard agglutination and Rose-Bengal tests which is followed by an increase of Ig G and Ig A in chronic stage of the disease (2,25). The anti-Brucella Coombs' test is of great value in the diagnosis of chronic NB. We observed that brucella agglutination and Coombs' tests were the two most common positive tests in CSF in our patients (three patients). As different from the study of Sanchez-Sousa, a positive reaction with Rose-Bengal test (one case) was less frequent than that obtained by the standard agglutination test (25). Case 1 had negative tests for brucella antibodies in CSF but the diagnosis was confirmed by isolation of Brucella species from CSF cultures. It is very unusual that a patient with meningeal inflammation and positive cultures for brucella in CSF had negative serological tests for Brucella antibodies (16). This case shows that CSF cultures for brucella are mandatory to exclude NB in cases with high suspicion of the disease. On the other side, positive CSF cultures are usually difficult to obtain (<20%), sometimes even in the presence of an apparent meningoencephalitis (7,8,16).

TPM-SMZ, rifampicin and doxycycline are the most commonly used antibiotics to treat brucellosis with a good intracelular and CNS penetration. Prolonged treatment (6 months) with a combination of these three antibiotics was used in our patients successfully. Hepatic and renal dysfunction developed only in one patient in the second week of the therapy. However, he tolerated well as the drugs were restarted. TIA discontinued in all patients in the very beginning of the therapy, although some of the abnormal findings in CSF remained unchanged. There is no agreement regarding the ideal duration of

treatment of NB, but it seems reasonable to continue therapy until the patient recovers or remains clinically stable, the CSF glucose return to normal, the CSF cell counts falls and CSF protein and antibodies begin to decrease.

Recognition of TIA and ischemic stroke due to brucellosis and its differentiation from other vascular diseases are not easy, particularly in the elderly patients with stroke risk factors such as hypertension, diabetes, atrial fibrillation etc. We suggest that NB should be always sought in young patients with TIA or ischemic stroke, especially if they do not have any additional risk factors for stroke and live in an endemic area for brucellosis, even if they do not have other

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EVALUATION OF CIRCUMCISION IN TURKEY

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SUMMARY

Aim: The aim of this study is to evaluate the frequency of the circumcision and complications due to this operation on young male starting their military obligation in Turkey and to investigate the performer, the place and the mean age.

Material and Metod: This study is a cross-sectional investigation proposed at Armor School and Training Division Command (Etimesgut-Ankara) between 04 and 28 March in 2002. 3625 privates enlisted in the Turkish Army are included in the study. During the general health examination of the participants, two urology specialists performed their urogenital examinations and noted down the results.

Results: The mean age of the privates was found 20.6±1.4. We found that 99.4% of the participants have been circumcised. The average age for circumcision was found 6.1± 3.2 years. Only 15.2% of the circumcisions were performed by a surgeon and 83.3% of them were executed at home. 24 participants (0.7%) had minor complications and 4 (0.1%) had major complications. In all the cases with complication, circumcisions were performed neither at a health center nor by a surgeon.

Conclusion: The circumcision is a traditional application in a Muslim country like Turkey and performed mainly by traditional practitioners. Therefore, the frequency of acute and chronic complications may increase due to nonphyscian operators. It is impossible to give up circumcision in a Muslim population, but unhealthy conditions must be prevented.

Key Words: Circumcision, Frequency and Complication

ÖZET

Türkiye'deki Sünnet Araştırması

Amaç: Bu çalışma askerlik görevine yeni başlayan genç erişkin erkeklerde sünnet olma sıklığının, sünnet olma yaşının, sünnet işleminin yapıldığı yerlerin, sünneti yapan kişilerin ve sünnet komplikasyonlarının saptanması amacıyla gerçekleştirilmiştir.

Gereç ve Yöntem: Çalışma 04-28 Mart 2002 tarihleri arasında Etimesgut Zırhlı Birlikler Okulu ve Eğitim Tümen Komutanlığında yürütülen kesitsel tipte bir araştırmadır. Çalışmaya adı geçen birliğe temel askerlik eğitimini almak üzere katılmış olan 3625 erbaş ve er dahil edilmiştir. Bu kişilerin birliğe katıldıkları anda yapılan genel sağlık muayeneleri sırasında iki üroloji uzmanı tarafından ürogenital muayeneleri yapılmış ve sonuçlar kaydedilmiştir.

Bulgular: Çalışmaya katılan erbaş ve erlerin yaş ortalamasının 20.6 ± 1.4 olduğu bulunmuştur. Katılımcıların %99.4'ünün sünnet olduğu, ortalama sünnet olma yaşı 6.1 ± 3.2 iken sünnet olanların sadece %15.2'sinin bir hekim tarafından bu işlemine tabi tutulduğu ve %83.3'ünde ise işlemin evde yapıldığı saptanmıştır. Diğer taraftan erbaş ve erlerin 24'ünde (‰6.6) minör 4'ünde (‰1.1) ise majör sünnet komplikasyonu saptanmıştır. Sünnet komplikasyonu saptanan vakaların tamamının hekim dışı personel tarafından ve sağlık kurumu dışında bir yerde sünnet edildiği bulunmuştur.

Sonuç: Türkiye gibi Müslüman ülkelerde geleneksel olarak uygulanan sünnet işleminin büyük bir kısmının hekim dışı personel tarafından ve sağlık kurumu dışında bir yerde gerçekleştirmiş olması bu işleme bağlı olarak ortaya çıkabilecek akut ve kronik komplikasyonların sıklığını artırmaktadır. İşlemin sağlıksız koşullarda ve yetkin olmayan kişiler tarafından yapılması önlenmelidir.

Anahtar Kelimeler: Sünnet, Sıklık, Komplikasyon

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Although circumcision is not performed always as a treatment method, it is a very common procedure in the world. For example, about %80 of American-born men are circumcised (1). Its benefits are reported commonly such as decreasing of the risk of penile cancer, urinary tract infections and sexually transmitted diseases (2-6). In contrary, others believe that it results in diminished sexual activity and sensitivity of glans (7-9). Some reported complications due to circumcision are one of the most important arguments against it. Thus performing circumcision is still controversial in modern medical area.

In this study, we aimed to document the frequency of the circumcision and complications due to this operation on young male starting military obligation in Turkey and investigate the person who performed, the place and the mean age of circumcision.

Table-1: Status of circumcision

Status of circumcision	Number	%
Circumcised	3602	99,4
Non-circumcised	23	0,6
Total	3625	100,0

Table-2: Age of circumcision procedure

Age	Number	%
0	58	1.6
1	219	6,0
2	284	7,9
3	362	10,0
4	258	7,2
5	386	10,7
6	546	15,2
7	390	10,9
8	303	8,4
9	242	6,8
10	248	6,9
11	113	3,1
12	104	2,9
13	29	0,8
14	18	0,5
15	22	0,6
16	5	0,1
17	11	0,3
18	4	0,1
Total	3602	100,0

Materyal and Metod

This study is a cross-sectional investigation proposed at Armor School and Training Division Command (Etimesgut-Ankara) between 04 and 28 March in 2002. 3625 new recruits who are enlisted in the Turkish Army are included in this study. As a standard procedure, every new recruit is examined when he starts his military obligation. During this general health examination, we included urogenital examination. Two urological specialists performed their urogenital examinations and noted down the results. In addition to this, the recruits were given a questionnaire including 17 questions. This questionnaire included socio-demographical information about privates such as age, marital status, educational status, city of birth, type of family, occupation, etc. In this questionnaire, it is asked whether they were circumcised or not. If they were circumcised, the performer, location and the age of circumcision were noted. All the statistical analyses were realized with SPSS 10.0 (SPSS Inc., Chicago, USA) statistical package program. Mean±sd was used for the descriptive statistics.

Results

The mean age of the privates was found 20.6±1. We found that 4. 99.4% of the participants have been circumcised (Table-1). The average age for circumcision was found 6.1± 3.2 years (Table-2). Only 15.2% of the participants were performed circumcision by a surgeon and 4.4% were performed by other medical person. 80.4% of circumcision were performed by traditional practitioners (Table-3). 521 (14,5%) privates had their circumcision at a health institution but 83.3% of circumcisions were performed at home (Table-4). We observed 28 complications due to circumcision (0.8%), 24 (0.7%) of which were minor complications (Figure-1 and Table-5), whereas 4 (0.1%) were major (Figure-2 and Table-6). Circumcisions were neither performed at a health center nor at a surgeon's office in cases who had complications.

Table-3: Person performing circumcision

Person	Number	%
Doctor	547	15,2
Other medical person	158	4,4
Traditional practitioners	2897	80,4
Total	3602	100,0

Table-4: Location of circumcision

Location	Number	%
Home	3002	83,3
Health institution	521	14,5
Others	79	2,2
Total	3602	100,0

Table-5: Minor complications due to circumcision

Complication	Number
Aesthetic problems	8
Incomplete circumcision	6
Keloid formation	4
Intradermal mass	3
Penile adhesion	3
Total	24

Table 6- Major complications due to circumcision

Complication	Number
Partial glanular amputation	2
Hypospadias	1
Penile curvatur/chordee	1
Total	4

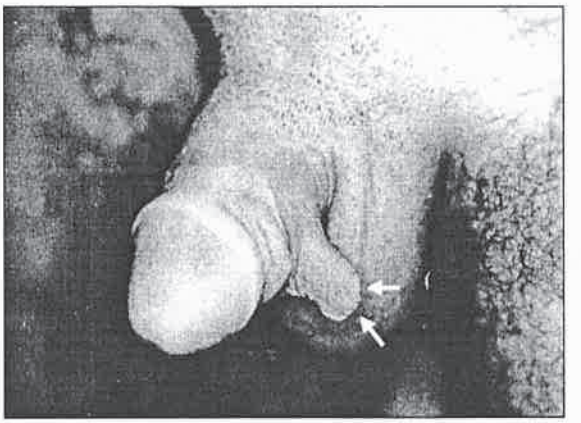

Figure-1: Minor complication due to circumcision (incomplete circumcision)

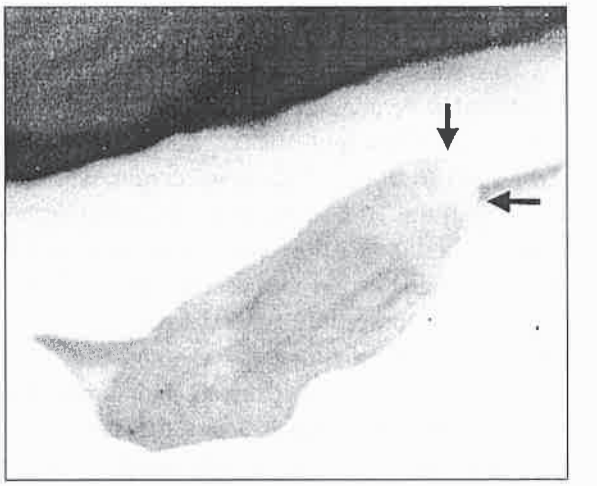

Figure-2 Major complication due to circumcision (partial glanular amputation)

Discussion

Circumcision has been described since antiquity (10). The practice of circumcision is thought to be at least 15.000 years old, but its origin and medical history are not well known. It is generally performed for religious grounds, medical necessity such as phimosis, recurrent balanitis, or aesthetic appeal (10). In the United States it is practiced virtually universally. Also there are some who accept circumcision as a preventive measure for carcinoma of the penis, carcinoma of the cervix, urinary tract infections, and sexually transmitted diseases (11).

There are a lot of circumcision techniques such as dorsal slit, Shield method, Sleeve method, and clamp methods (Gomco clamp, Sheldon clamp, Plastibell clamp, Winkelman clamp, Tara clamp, Yellen clamp, Bronstein clamp etc.). Whatever a surgeon chooses a technique for circumcision, the aim of circumcision is the same: To excise sufficient foreskin to leave the glans uncovered. Guillotine method, which is not included in classic textbooks, is one the most commonly performed method for circumcision. In this method, the glans is fixed with fingers, and a clamp is placed on prepuce carefully. After the removal of the skin above the clamp, mucosa and submucosa are sutured. Despite it is not clear; we think that Guillotine method is the most commonly performed method for circumcision in Turkey.

Whether it is done for ritual, traditional or medical reasons, circumcision remains the most common operation performed on males worldwide. In Turkey as a Muslim country, the

basic reason for circumcision is religious grounds and circumcision is performed as a religious ceremony. Approximately, 800.000 male children are born each year in Turkey and 95% of them are Muslims (12). Thus circumcision is one of the most commonly performed procedures in Turkey. In Muslim countries like Turkey circumcision is generally undertaken by a person who is not medically trained. We think this creates the main reason for complications of circumcision. As circumcision is generally carried out by unqualified traditional practitioners, variable circumcision characteristics cannot be determined easily. The person who perform the operation, a physician or a traditional circumciser, may affect their health as well.

Military duty is obligatory for every male in Turkey and all males are examined before starting Military obligation in a routine fashion. We conducted our study in this group. In our study, we determined that only 15.2% of the participants were circumcised by a surgeon. Another important finding is that 83.3% of them were executed at home instead of a medical institution. In Turkey most of Muslim boys generally undergo circumcision before puberty. Supporting this situation, we found the average age of performing circumcision as about 6 years. In contrast to America and Europe countries, where circumcision is performed in the neonatal period, it is performed at older ages in Turkey, and timing may affect the psychosocial well being of males.

Despite the fact that circumcision is a relatively simple operation, complications can occur ranging from trivial to tragic. The argument against circumcision is based on the surgical complications of this intervention in children. Many complications due to circumcision have been cited in different reports. Complication rate after circumcision is reported to be 0.2-5% in the literature (2,13). Reported complications after circumcision include hypospadias, glanular amputation, urethral fistulae, penile adhesions, keloid formation, haemorrhage, meatal stenosis, infection, incomplete circumcision, penile oedema, urinary retention, gangrene of the penis and intradermal mass (13,14,15). Latifoglu et al. found that urethral fistula formation was the most common complication of circumcision (12). In his series, medically unqualified traditional itinerant circumcisers caused 92.5% of the complications. In our study, we found the most common complication of circumcision as aesthetic problems. 24 (0.8%) minor and 4 (0.1%) major complications were noted. In all the cases with a complication, circumcisions were neither performed at a health center nor by a surgeon. Penile amputation at any level is rare but it is the most seriously reported complication of circumcision (16,17). We determined 2 partial glanular amputation in our series. To prevent these complications, practice of any surgical operation by unqualified practitioners should be abandoned and significant punishment should be considered.

Conclusion

Circumcision is usually a simple and safe intervention with minimal complication if performed correctly. Most complications result from unqualified non-physician persons. To give up the circumcision is impossible in a Muslim population; but we should prevent unhealthy conditions during this procedure. Ideally, each male planning to undergo circumcision should be evaluated beforehand by medically trained professionals and circumcision should be carried out in aseptic conditions at a medical center by surgeons.

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TOTAL HIP ARTHROPLASTY IN THE NEGLECTED DEVELOPMENTAL DISLOCATION OF THE HIP.

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SUMMARY

We evaluated total hip arthroplasty in patients with neglected developmental dislocation of the hip with regard to surgical method and modifications, problems encountered during surgery, and follow-up results. A total of 25 hips (Hartofilakidis type 3, high dislocation) of 22 patients (22 women; mean age 44 years; range 28-61 years) who underwent total hip arthroplasty were clinically and radiologically evaluated. In all cases, cementless acetabular components were placed in the true acetabulum. Only one acetabula required structural autograft. Cementless stems were used on the femoral side. A subtrochanteric osteotomy was performed in 23 hips. The mean follow-up period was five years (range 2 to 10 years). The scale of Merle d'Aubigne and Postel, as modified by Charnley was used to evaluate the clinical results. Pain improved from a mean of 2.3 preoperatively to 5.7 postoperatively. Function improved from 2.3 to 4.5 and mobility from 2.3 to 4.4 at the final follow-up evaluation. No acetabular autograft resorption or non-union were observed. Intraoperatively femoral fissure occurred in 3 cases. One sciatic nerve palsy occurred. Brooker type IV heterotopic ossification was observed in one case. Three polyethylen wear, 1 DVT, 2 osteolysis were observed during the follow-up.Total hip arthroplasty proved successful in neglected developmental dislocation of the hip.

Key Words: *Total Hip Arthroplasty, High Dislocation, Hip, Shorthening Osteotomy*

ÖZET

İhmal Edilmiş Gelişimsel Kalça Çıkığında Total Kalça Artroplastisi

İhmal edilmiş gelişimsel kalça çıkıklı hastalarda uygulanan total kalça artroplastisinin cerrahi teknikleri, modifikasyonları, ameliyat sırasında karşılaşılan problemler ve takip sonuçları değerlendirildi. Total kalça artroplastisi uygulanan 22 hastanın (22 kadın, ortalama yaş 44; dağılım 28-61) 25 kalçası (Hartofilakidis tip 3; yüksek çıkık) klinik ve radyolojik olarak değerlendirildi. Tüm vakalarda çimentosuz asetabular kaplar gerçek asetabuluma yerleştirildi. Sadece bir vakada asetabuluma strüktürel otogreft kullanıldı. Femoral tarafta çimentosuz stemler kullanılmıştı.23 kalçada subtrokanterik kısaltma osteotomisi uygulandı. Ortalama takip süresi 5 yıl (dağılım; 2-10 yıl) olan kalçaların klinik sonuçları Charnley tarafından modifiye edilen Merle d'Aubigne ve Postel skalasına göre değerlendirildi. Ağrı skoru ameliyat öncesi 2.3 den ameliyat sonrası 5.7'ye yükselirken son takiplerde fonksiyon puanı 2.3 den 4.5'a, mobilite ise 2.3 den 4.4'e yükseldiği saptandı.Asetabular otogreftte rezorpsiyon yada osteotomi alanında kaynamama görülmedi. 3 femurda intraoperatif fissür gelişti. Ameliyat sonrası bir hastada peroneal sinir felci, 1 hastada Brooker tip IV heterotopik ossifikasyon, 1 hastada DVT, 2 kalçada osteolizis, 3 kalçada ise polietilen aşınması saptandı. İhmal edilmiş kalça çıkıklarında total kalça replasmanı uygulaması zorluklara rağmen başarılı bir girişimdir.

Anahtar Kelimeler: *Total Kalça Artroplastisi, Yüksek Çıkık, Kalça, Kısaltma Osteotomisi*

Total hip arthroplasty for the group of disorders ranging from simple acetabular dysplasia to high dislocation, is a technically difficult procedure with diverse choice of methods. The deformed anatomy causes many problems both at the acetabulum and the femur. These include abnormal bony structures, abnormal location of the hip center, leg-length discrepancy, abnormal neurovascular structures and abductor muscle insufficiency (1-9). Of these, the most common problem poor bone stock at the acetabular side (1,4,10) and small

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intramedullary cavity of the femur (4). Good technical solutions have been developed for all stages of the disease and good or excellent results can achieved in most cases (2-20). The surgical technique of a simple acetabular dysplasia is different from that of a high riding dislocation of the hip. Femoral shortening osteotomy that is not needed for simple acetabular dysplasia or low dislocation is mostly inevitable in high dislocation. There is no consensus on reporting the clinical and radiological results because of the great variety in the surgical techniques.

We aim to report the results of the total hip arthroplasties on a series of patients with developmental high dislocation of the hip managed with the same technique, and the problems encountered during the procedures are discussed.

Patients and Methods

The adult hip dislocations and dysplasias have been classified by Eftekhar (21), Crowe et al.(2), Hartofilakidis et al.(8), Kerboul et al.(22) and Mendes et al.(23). The most practical and convenient one is the Hartofilakidis and associates classification (HC). For this reason, we favor this classification system over the others. According to this classification (8), Type 1 is the dysplastic hip and the femoral head remains in the true acetabulum. Type 2 is the low dislocation and the femoral head is in the false acetabulum, but the inferior part of the head is in contact with the true acetabulum. In type 3, also known as high dislocation, the head is completely in the false acetabulum and there is no contact with the true acetabulum. While HC Type 1 corresponds to Crowe Type I and II, HC Type 2 to Crowe Type III and HC Type 3 to Crowe Type IV.

To 25 hips of 22 patients with developmental high dislocation of the hip, total hip replacements (THR) were performed (Table 1). All total hip replacements procedures were performed at the Ibni Sina Hospital from 1992 through 2000. The indications for arthroplasty were severe hip pain, with considerable difficulty in walking and in performing activities of daily living. All of the patients had Hartofilakidis type 3 (high dislocation) preoperatively. Patients with dysplasia were not included in this study. In five cases Schanz osteotomy had been performed previously on the same hip. All the patients were women and the average age at the time of the operation was forty-four years (range, twenty-eight to sixty-one years). Each patient was evaluated with the hip-rating system of Merle d'Aubigne and Postel,as modified by Charnley (24). Trendelenburg's sign of pelvic instability was also recorded. Preoperatively and postoperatively radiographs were taken in standing antero-posterior and in the frog-leg lateral positions. The follow-up radiographs were evaluated for the change in component position, radiolucencies at the implant-bone interface and screw breakage. We referenced the location of the center of the femoral head to a line drawn through the teardrops (25). The vertical height was measured perpendicular to this reference line. The horizontal displacement of the center of the femoral head was measured along this line as the distance from the teardrop. Prophylactic antibiotic therapy was given one hour before operation and continued for 48 hours. Thromboembolic prophylaxis included low molecular weight heparin (subcutan, approximately 15 days), early mobilization, encouragement of active leg movement and anti-embolic stockings.

Surgical Technique

The operative procedure was carried out through a direct lateral approach (26) with the patient in supine position. In the type 3 (high dislocation) cases no difficulty was encountered while dislocating the head, as the femoral head was already in the false acetabulum. The location of the true acetabulum was difficult to determine in many cases, but following the elongated and attenuated capsule was often helpful. The true acetabulum was narrow and shallow and thus required careful exposure. The anterior wall generally was thin and deficient, and room could be gained by curetting toward the thicker posterior wall. The hypoplastic true acetabulum was enlarged and deepened with the use small reamers (forty to forty-two and four diameters). In the type 3 hip, the inferior wall of the false

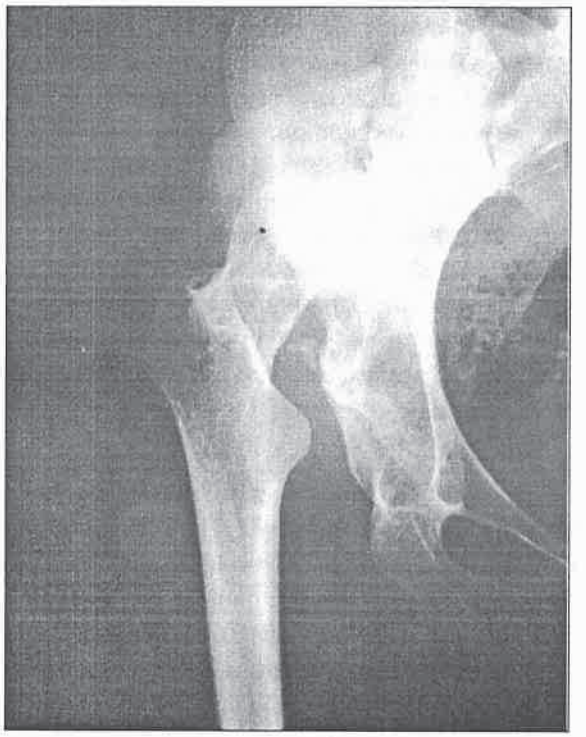

Fig 1A: Preoperative radiograph.

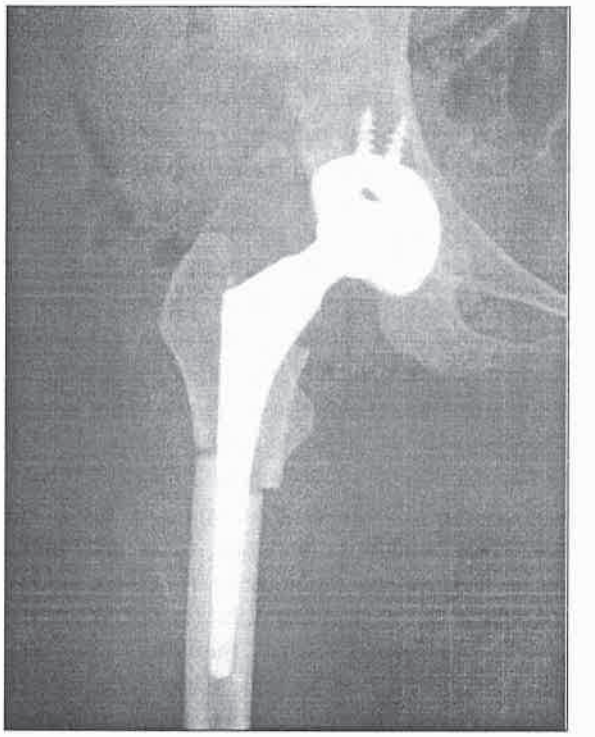

Fig 1B: Immediate postoperative radiograph after a subtrochanteric shortening step cut osteotomy. An uncemented hydroxylapatite coated stem will provide fixation of both proximal and distal segments.

Fig.1A-B: High dislocation of the right hip in a 44-year-old-woman.

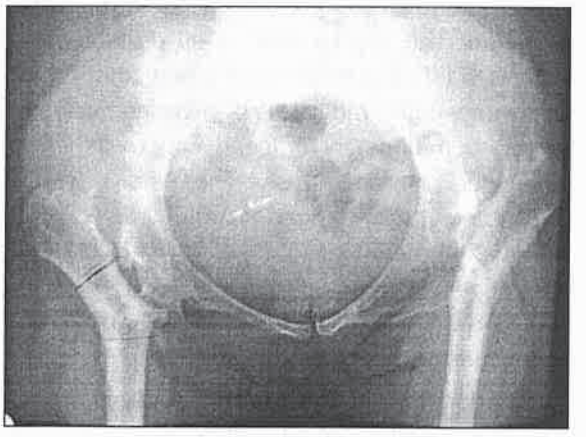

Fig 2A: Preoperative anteroposterior radiograph of the pelvis and hips.

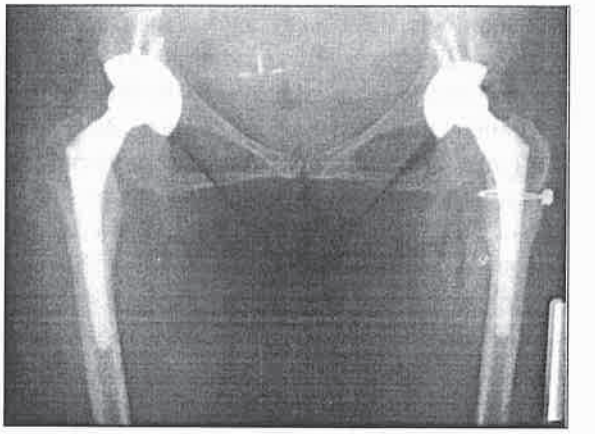

Fig 2B: Bilateral total hip arthroplasties were performed for disabling pain. Both acetabulae were reconstructed with noncemented hydroxylapatite coated shells.The acetabular cups had been placed in the true acetabulum. Bilaterally, transvers subtrochanteric osteotomies were performed and a cementless femoral components were used. Five years postoperatively, the patient had good clinical and radiographic results,with union of the femoral osteotomies.

Figs.2A-B: A 38-year-old woman with high developmental hip dislocation bilaterally. Right and left hips treated by Schanz osteotomy 13 years previously.

acetabulum is the superior wall of the true acetabulum. There are two main points that are crucial in the procedure; one of them is to protect the bone bridge between the two acetabuli; and the other is to ream the posterior portion of the acetabulum more than the anterior so that the insufficient anterior wall will be protected during the preparation. The acetabular component was placed true acetabulum in all patients. In one case more than 70% of the cup remained uncovered and thus the femoral head was used as a graft and fixed with two screws. The largest uncemented cup possible should be used. The most suitable cup sizes for type 3 dislocated hips was usually 40-42-44 or 46 mm. As the bone quality is mostly rather bad, cups permitting screw fixation are generally more advantageous regardless of the primary stability. The diameter of the cup is usually small; therefore, a 22 mm head should be used to leave room for a liner of satisfactory width. In case of using a system permitting metal-to-metal articulation, a 28 mm head can be used. Thirty-two-millimeter heads were used in 2 of the cases, 28 mm heads were used in 12 (3 of these were metasul) and 22 mm heads were used in 11 cases.

If a subtrochanteric osteotomy was planned preoperatively, it is best to perform the osteotomy at the beginning of the operation, so that the entrance to the acetabular inlet at the level of the trochanter minor would be easier. After the placement of the acetabular component the femoral component is inserted into the proximal part of the femoral bone and the hip is reduced. The amount of shortening required can then be determined by overlapping the proximal and the distal fragments of the femur and appropriate amount of bone is resected from the distal segment. A subtrochanteric osteotomy was performed in 23 hips. If an osteotomy such as a Schanz osteotomy had been performed formerly, both shortening and correction can be achieved by the procedure. In our series, a step-cut osteotomy was performed in 3 hips and a transverse osteotomy in all of the rest. Fixation and rotational stability can be achieved by screw and metal plates, tension band technique or by using a long-stem prosthesis. We used the tension band technique for two of the transverse osteotomies and screw and plates for another. We relied on the femoral stem for stability of the rest. Uncemented components were used for all of the femoral side (Table 1). Soft tissue release was done only by sectioning the linea asperea. Aggressive tissue release should be avoided in cases that a shortening osteotomy is performed. After the operation the patients were ambulated without bearing weight. Partial weight bearing was allowed at six weeks and full weight bearing at 12 weeks.

Results

The average duration of follow-up was five years (range, two to ten years). The scale of Merle d'Aubigne and Postel, as modified by Charnley was used to evaluate the clinical results. Pain, function and mobility were assessed separately. Pain improved from a mean of 2.3 preoperatively to 5.7 postoperatively. Function improved from 2.3 to 4.5 and mobility from 2.3 to 4.4 at the final follow-up evaluation. All patients had a typical Trendelenburg limp before the arthroplasty. Postoperatively, Trendelenburg limp was moderate in nine (36 %) and slight in sixteen hips (64%). The center of the femoral head was moved inferiorly and medially at the time of the operation. The average horizontal displacement decreased fifty-five millimeters (range, thirty-nine to seventy-eight millimeters) preoperatively to twenty-six millimeters (range, twenty to sixty-five millimeters) postoperatively. The average height of the center of the femoral head decreased from seventy-two millimeters (range, forty-nine to 107 millimeters) preoperatively to forty-six millimeters (range, thirty-five to sixty-nine millimeters) postoperatively.

Intraoperatively, during the insertion of the acetabular component an acetabular medial wall fracture occurred in one of the cases. The medial wall was grafted with the femoral head. On postoperative radiographic evaluation the cup was seen to be seated more vertical than should be. At the postoperative eighty months polyethylene wear was encountered. A second case of premature polyethylene wear happened at the postoperative seventy- two months. The

Table 1: Data on the Twenty-Two Patients

Case #	Gender,age(yr)	Side	Type	Previous Osteotomy	True/False Acetabulum	Graft	Head (mm)	Femoral Osteotomy	Prosthesis Type	Complications	Follow-up (months)
1	F,60	L	3	No	True	No	28	No	Balgrist/Zweynmüller	No	87
2	F,63	R	3	No	True	No	32	Yes	Banjica	Aseptic loosening No revision	127
3	F,61	L	3	No	True	No	32	Yes	Banjica	Early postop dislocation, PEW* - revision	95
4	F,45	R	3	No	True	No	22	Yes	Plasma/Biocontact	No	81
		L		No	True	No	28	Yes	Plasma/Biocontact	No	64
5	F,55	R	3	Yes	True	No	22	Yes	Securfit	No	54
		L	3	Yes	True	No	22	Yes	Securfit	No	44
6	F,55	L	3	No	True	No	22	Yes	Securfit	Nerve paralysis FR** (28 months)	51
7	F,42	L	3	No	True	No	28(metasul)	Yes	Standart cup/Cone	No	61
8	F,35	L	3	No	True	No	22	Yes	Plasma/Biocontact	HO*** Aseptic loosening No revision	66
9	F,28	L	3	Schanz	True	No	28	Yes	ABG	PEW (72 months) No revision	120
10	F,53	L	3	No	True	No	28	Yes(step-cut)	Bimetric	No	73
11	F,62	L	3	Schanz	True	No	28	Yes	Expantion/Wagner	No	78
12	F,53	R	3	No	True	No	22	No	ABG	Intraop acetabular Medial wall fracture, PEW No revision	98
13	F,36	L	3	No	True	No	28	Yes	Expantion/Cone	No	28
14	F,38	R	3	Schanz	True	No	22	Yes	Securfit	No	55
		L	3	Schanz	True	No	22	Yes	Securfit	Intaop FF****	42
15	F,49	L	3	No	True	No	22	Yes	Securfit	No	34
16	F,32	L	3	No	True	Yes	28(metasul)	Yes	Expantion/Cone	Non-union	41
17	F,40	R	3	No	True	No	28	Yes	Securfit	Intraop FF, DVT***** (3 weeks)	63
18	F,37	L	3	No	True	No	28(metasul)	Yes	Expantion/Cone	No	54
19	F,48	L	3	Schanz	True	No	22	Yes(step-cut)	Securfit	No	67
20	F,55	L	3	No	True	No	28	Yes	Expnation/Cone	No	42
21	F,44	R	3	No	True	No	22	Yes(step-cut)	Securfit	No	44
22	F,49	L	3	No	True	No	28	Yes	Expantion /Cone	No	45

PEW* Polyethylene Wear
FR** Full Recovered
HO*** Heterotopic Ossification
FF**** Femoral Fissure

third case having polyethylene wear needed a revision surgery. Femoral fissure occurred in 3 cases and was fixated using cerclage wire in 2. Heterotopic ossification was seen in only one patient and resulted in moderate limited hip motion. Peroneal nerve paralysis, which completely resolved in twenty-eight months, was observed in one case. Osteolysis (in all zones) developed in 2 hips. In one case deep venous thrombosis developed at the third week and completely responded to treatment. There was no infection, or abductor contracture.

Discussion

Total hip arthroplasty is a difficult procedure to perform on high hip dislocations. The main problems and the complications should be well known before performing a THA. One of the most important issues is where and how the acetabular component should be placed. Charnley and Feagin (1) therefore believe that total hip replacement is contraindicated in these patients, while Justy et al. (19) prefer to place the cup in the false acetabulum. Although the true acetabulum is hypoplastic and shallow, it still is much better, considering its bone stock, than the false acetabulum. Placing the cup into the true acetabulum is the most accepted technique regarding the literature (1,4,21,23). Obtaining satisfactory acetabular cup coverage is the key step. For most cases, this necessitates only deeper reaming and use a small diameter (forty, forty-two) acetabular component that is porous-coated. The small components can be covered completely in most patients. Because the components are initially stabilized with screws, small portions of the components can be left uncovered and nonstructural bone graft can be added to fill the uncovered areas. The reason for preferring uncemented cups Is that there is a possibility of screw fixation other than primary fixation. We believed that 70% of the cup should be covered with intact host bone (18,27). If more than 30% of the cup is uncovered, consideration should be given to use of bulk autograft or allograft. The femoral head was applied as an autogenous graft in one case using the method of Harris et al. (7) to compensate for the severe superolaterale wall deficiency of the true acetabulum. This technique was very successful for the short term and allowed total hip replacements even in patients with severe congenital hip dislocation (7). However, long-term results have shown unacceptably high loosening rates of the acetabular components with structural autugrafting and allografting (6,19,27).

Another technique is the high hip center technique (28). This is a convenient technique based on the principle of placing a small sized uncemented cup without using a graft. On the other hand, the main disadvantage of the technique is that the loosening of the cup is encountered more than with other methods and the possibility of dislocation is much higher (29,30) . When this cup is placed, lengthening can be performed on the femoral component. As the bone stock is not generally restored in these procedures, it may cause difficulty in future surgeries. Despite all these disadvantages, the method can be used in patients who have enough bone stock and when the difference between the length of the two legs is 2-3 cm. In selected cases, this technique has been used in our other series.

We have no experience in the treatment of high dislocation of the hip with a third technique, which is the centralization of the cup that is also named as cotyloplasty (4,5,20). Fifteen of 17 hips were found to have an excellent results after a relatively short-term follow-up (mean,37 months) (5). Hartofilakidis et al. (20) reported the results at a mean of seven years (2 to 15 years) after cotyloplasty in 86 hips in 66 patients. Eigtht-one of the 86 hips (94%) had a good or excellent results, and only 2 acetabular components had to be revised during the study period.

Alternatives include the use of cement to augment the acetabulum (13), and the use of a reinforcement ring (30). Bipolar prostheses have also used in patients with dysplastic asetabulum but may lead to high rates of femoral loosening and acetabular erosions (31).

The difference in length is an important problem encountered especially in unilatera

high dislocation of the hip. This brings the question of how much lengthening can be achieved. First of all, the patient should be acknowledged about the amount of lengthening that can be done. Maximal amount of safe lengthening is 4 cm (18,32). If a lengthening more than 2 cm is to be done during the operation, the trial prosthesis should be placed and the tension on the sural nerve should be tested. Brutal dissection exposing too much of the nerve and causing devascularization should be avoided, especially if a posterior incision is being used. An alternative method is the wake-up test, but the patient should be informed preceding the operation. The dorsiflexion of the first toe is more reliable than its plantar flexion. In more complicated cases SSEP should be preferred. If the tension on the nerve is too much there are two choices. The acetabular cup can be placed higher or a subtrochanteric osteotomy can be performed. This points out to the importance of preoperative planning. In our department, if more than 4 cm of lengthening will be needed, we have a consensus of performing a subtrochanteric osteotomy at the beginning of the operation. The main aim of the operation is to place the acetabulum at its true, original level; therefore, instead of releasing all of the tissues, we believe that performing a shortening osteotomy and minimizing the tension on the nerve is a better method. If aggressive releasing is conducted, as the lengthening amount will be significant, and the risk of nerve injury will increase. Nerve palsy has occurred in one of our cases that had undergone a shortening procedure. Full recovery occurred in 28 months.

The subtrochanteric osteotomy can be done in different ways (14,33,34). It can be transverse or step-cut in order to achieve rotational stability, it can be oblique or chevron shaped. However, the other methods are technically more difficult than the transverse osteotomy. The stability can be achieved by screws, metal plates, tension band technique, cortical onlay grafts or by long stem prostheses (16,17). The most important problems are rotational stability and nonunion.17,34 In this series, tension band technique was used for 2 patients and plate and screws in another. The remaining distal femoral medulla after the shortening osteotomy is narrow and in most cases the femoral stem inserts tightly and in satisfactory length abolishing the need for extra fixation techniques (14,17,19).

In the evaluation of hip arthroplasty in dislocated hips is the function of the hip abductor muscles. In this series, all the patients had a preoperative Trendelenburg limp. Postoperatively, Trendelenburg sign was moderate in nine hips (36 %) and slight in sixteen hips (64%). The tension of the muscle was then increased, and we assume that the restoration of the biomechanics of the gluteus medius is the explanation for the slightly appearance of the Trendelenburg limp in the most cases (14). In this patients still had insufficient of the abductor muscles, but none needed external support.

As a conclusion it can be stated that, although technically difficult, THA gives successful results in the treatment of high hip dislocations. The placement of the cup into the true acetabulum, lengthening the extremity being careful to tightness of the nerve, because the disease is a problem of a relatively younger group, preferring uncemented components, and a good preoperative planning are important in achieving successful results.

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METABOLIC, ENDOCRINE AND CLINICAL FINDINGS IN A CASE WITH ALSTRÖM SYNDROME

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SUMMARY

Alström syndrome is an autosomal recessive disorder which is characterized by excessive insulin resistance. Truncal obesity, sensorineural deafness, acanthosis nigricans and retinal degeneration are the clinical features of Alström syndrome. In addition, hypogonadism, short stature, glomerulotubular dysplasia, benign cardiomyopathy, hyperlipidemia, mental retardation and hepatic dysfunction have been reported in the medical literature. Here we report on a case with Alström syndrome and bronchial asthma. The patient, who had been followed up for bronchial asthma diagnosed at the age of 2. A 7,5 years old girl was referred to our clinic because of obesity. The family history was significant for her parents being second degree relatives. Her physical examination revealed truncal obesity, visual loss, hearing loss and acanthosis nigricans. In developmental evaluation, border line mental retardation was noted. Her laboratory tests showed increased hepatic transaminases, hyperlipidemia, exaggerated hyperinsulinism and a normal oral glucose tolerance test. Audiological evaluation revealed mild degree sensorineural hearing loss and ophthalmologic examination revealed retinal degeneration. The patient had typical characteristics of Alström syndrome. This syndrome is one of the syndromic causes of Type 2 diabetes mellitus of childhood and therefore should be kept in mind.

Key Words: *Alström Syndrome, Bronchial Asthma, Diabetes Mellitus*

ÖZET

Alström Sendromlu Bir Olguda Metabolik ve Endokrin Bulgular

Alström sendromu, aşırı insülin direnci ile karakterize, otozomal ressesif geçişli bir hastalıktır. Trunkal obezite, sensorineural sağırlık, akantozis nigrikans ve retinal dejenerasyon bu sendromun klinik belirtileridir. Bu belirtilerle birlikte; hipogonadizm, kısa boy, glomerulotubuler displazi, benign kardiyomiyopati, hiperlipidemi, mental retardasyon ve hepatik disfonksiyonun görüldüğü olgular literatürde bildirilmiştir. Astımın eşlik ettiği Alström sendromlu bir olguyu sunuyoruz. İki yaşından beri astım tanısı ile izlenen hasta 7.5 yaşında iken obesite nedeniyle kliniğimize refere edildi. Aile öyküsünden anne ve babanın ikinci dereceden akraba olduğu öğrenildi. Hastanın fizik incelemesinde trunkal obesite, görme kaybı, işitme yetersizliği ve akantozis nigrikans, psikiyatrik muayenede de sınırda mental retardasyon tesbit edildi. Laboratuvar tetkiklerinde karaciğer transaminazlarında yükseklik, hiperlipidemi ve hiperinsülinizm bulunurken oral glukoz tolerans testi normal bulundu. İşitme testinde sensorineural tipte işitme yetersizliği, oftalmolojik muayenede retinal dejenerasyon tesbit edildi. Hastamız Alström sendromunun karakteristik özelliklerini taşırken; eş zamanlı astımı da bulunmaktadır. Alström sendromunun karakteristik belirtileri olup, çocukluk çağında görülen Tip 2 diabetes mellitusun sendromik sebeplerinden biri olduğu vurgulanmaya çalışılmıştır.

Anahtar Kelimeler: *Alström Sendromu, Astım, Diabetes Mellitus*

Alström syndrome is a rare autosomal recessive disorder characterized by truncal obesity, sensorineural deafness, retinal degeneration, acanthosis nigricans and diabetes caused by excessive insulin resistance (1). In addition, hypogonadism, short stature, glomerulotubular dysplasia, benign cardiomyopathy, hyperlipidemia, mental retardation and hepatic disfunction have been reported in previously (1-5). Bronchial asthma has been defined in only a few patients (4). The genetic locus of the Alström syndrome has been mapped to 2p12-13 chromosomal zone (6-8). Inheritance pattern is autosomal recessive.

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We report on a 7.5 year old girl who has the typical characteristics of Alström syndrome and also has additionally asthma.

Methods

Relative body mass index (RBMI) was used to determine obesity. This index was calculated with the formula; RBMI: [Patient's BMI (kg/m^2) / predicted BMI (kg/m^2)] X 100. Olcay Neyzi's Turkish standarts were used to predict BMI (10). The values over 120 was accepted as obese.

To determine the metabolic profile; serum insulin, glucose measurements and oral glucose tolerance test were performed. Blood samples were obtained before and 30,60,90 and 120 minutes after glucose load (1.75 g of glucose per kilogram of body weight, maximum 75 g). Fasting insulin / glucose ratios and 120 minutes after loading insulin / glucose ratios were calculated and ratios over 0.4 were accepted as hyperinsulinemia (11)

The serum insulin concentrations were measured by using radioimmunassay (RIA) method with diagnostic system laboratory (DSL) kit. The serum glucose concentrations were determined with SIGMA glucose kit.

L-Dopa stimulation test was done for testing growth hormone. Blood samples were obtained before and 45, 90 minutes after 500 mg of L-Dopa taken orally. The serum growth hormone (GH) and IGF-I were measured by using RIA method with DSL kits.

Case Report

O.C. 7.5 years old girl was admitted to our clinic for obesity. She had been followed up because of bronchial asthma since she was 2 years old. Her family history was significant for her parents being second degree relatives. Her mother was 36 years old and healthy, father was 44 years old and obese. She had a sibling who had died because of heart failure. She has had hearing loss and visual impairment since birth. Her physical examination revealed truncal obesity, visual loss, hearing loss and acanthosis nigricans in the cervical and axillar areas (figure 1,2 – Table I) . Patient's body weight was 44.5 kg

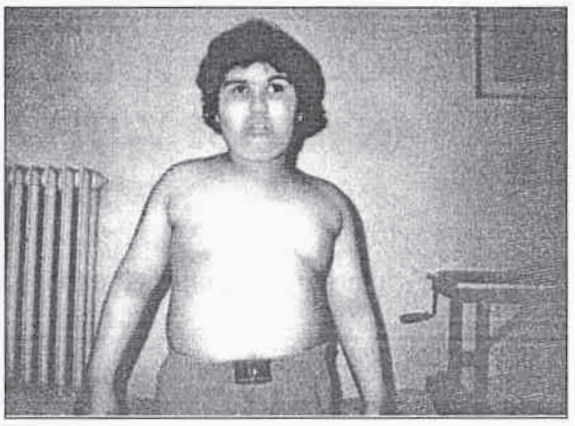

Figure 1: Truncal obesity in the patient

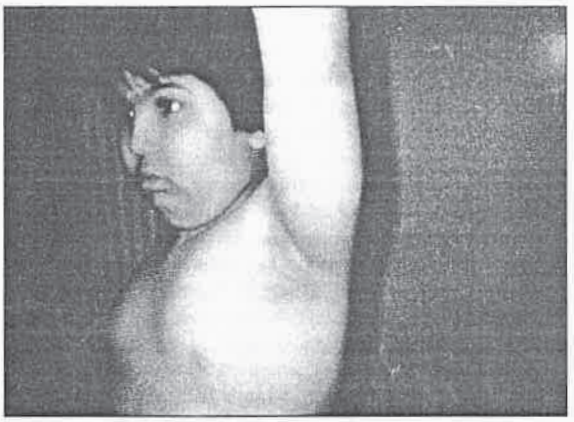

Figure 2: Acanthosis nigricans in the patient

Table 1: Summary of the patient and Alström syndrome

ALSTRÖM SYNDROME	CASE
TRUNCAL OBESITY	+
ACANTHOSIS NIGRICANS	+
RETINAL DEGENERATION	+
MENTAL RETARDATION	+
SENSORINEURAL DEAFNESS	+
HYPERINSULINISM	+
TYPE 2 DIABETES MELLITUS	?
HYPERLIPIDEMIA	+
HYPOGONADISM	?
HEPATIC DYSFUNCTION	+
CARDIOMYOPATHY	-
GLOMERULOTUBULAR DYSPLASIA	-
ASTHMA	+
SHORT STATURE	-

(over 97 %), height was 133 cm (97 %), body mass index (BMI) was 25.2, relative BMI was 156 and bone age was compatable with 7 years and 10 months.

Laboratory tests revealed exaggerated hyperinsulinism (fasting insulin:207.2 mIU/ml, postprandial insulin: 542.4 mIU/ml) and a normal oral glucose tolerance test which ruled out diabetes (SUM glucose: 316 mg/dl) (Table II).

Her audiometric evaluation revealed a mild degree of sensorineural hearing loss and her ophthalmologic examination under general anesthesia displayed retinal degeneration.

Inspite of normal somatic growth, low growth hormone response to L-Dopa stimulation was detected (GH peak:1.8 ng/ml); but IGF-1 level was with in the normal ranges (IGF-1:132 ng/ml 5-50 percentile) (Table 2). In psychiatrical examination border line mental retardation was detected.

She had bronchial asthma despite negative skin prick test reactivity to a panel of common aeroallergens (house dust mites, pollens, mold, weed, feather mixture) and elevated specific IgE levels against a standard set of allergens.

Her hepatic transaminase enzymes were slightly elevated (ALT:61 U/L). Her lipid profile was hyperlipidemic (triglyceride: 173 mg/dl, total cholesterol:256 mg/dl, HDL cholesterol:38 mg/dl, LDL cholesterol:183 mg/dl, VLDL cholesterol:35 mg/dl, total cholesterol/HDL cholesterol:6.73,) . Abdominal USG revealed an increase in liver paranchyme echogenity (steatosis), hepatomegaly and increase in bilateral renal paranchyme thickness and peripyramidal echogenity.

Table 2: Endocrinologic evaluation of the patient

ENDOCRINOLOGIC EVALUATION		
METABOLISM OF GLUCOSE	FI*:207.2 mIU/ml ↑ FG*:36 mg/dl FI/FG:5,75 >0,4 FG/FI:0,17 <7	PI**:542.4mIU/ml ↑ PG**:58 mg/dl PI/PG:9,35 >0,5 PG/PI:0,1 <7
	oral glucose tolerance test SUM glucose:316 mg/dl <400mg/dl normal glucose curve	NO DIABETES MELLITUS
DYSLIPIDEMIA	Triglyceride: 173 mg/dl Total cholesterol:256 mg/dl >200 HDL cholesterol:38 mg/dl LDL cholesterol:183 mg/dl >130 VLDL cholesterol:35 mg/dl Total cholesterol/HDL cholesterol:6.73 >4	
Hypotalamo-pituitary-IGF-1 axis	GH peak to L-Dopa stimulation test:1,8ng/ml ↓ IGF-1:132 ng/ml (%5-50)	

*FI: Fasting Insulin
*FG: Fasting Glucose
**PI: Postprandial Insulin
**PG: Postprandial Glucose

Discussion

Alström syndrome is a rare autosomal recessive disorder characterized by obesity, sensorineural deafness and retinal degeneration which all appear during the first decade (1). The genetic locus of the Alström syndrome has been mapped to 2p12-13 chromosomal zone (6-8). In our patient, initial manifestations were bronchial asthma, hearing impairment, visual problems and obesity. Obesity, visual problems and hearing impairment had presented during the first year of life. The age of onset of asthma was two years.

Diabetes caused by insulin resistance occurs later, usually in the second and third decades (1). In our patient; hyperinsulinism was exaggerated and the oral glucose tolerance test was normal, meaning that she wasn't diabetic yet. Another manifestation of exaggerated hyperinsulinism was acanthosis nigricans.

As before defined for obesity, in this syndrome hypotalamo-pituitary IGF-1 axis is also generally supressed but somatic growth retardation is not detected. In our patient somatic growth was normal. Low growth hormon response to L-Dopa stimulation was detected. IGF-1 level was with in the normal ranges, therefore normal somatic growth can be explained by hyperinsulinism and normal IGF-I concentrations (2).

Patients with Alström syndrome usually have dyslipidemia with hypertriglyceridemia and normal cholesterol levels. Our patient also had dyslipidemia but with hypercholesterolemia and mild elevated triglyceride levels.

Liver patologies extending from elevated transaminase levels to cirrhosis have been reported in the literature (5,12). Awazu and et al reported two siblings with liver dysfunction. One of the siblings had elevated liver enzymes. Fatty infiltration, piecemeal necrosis and infiltration of lymphocytes were seen in liver biopsy. Other sibling had high levels of GGT since he was 10 years old and developed liver cirrhosis during follow-up. Our patient's hepatic transaminase enzymes were slightly elevated. In abdominal USG there was an increase in the liver paranchyme echo (steatosis) (12). Liver biopsy will be considered in the future according to follow up.

Benign cardiomyopathy is mostly seen at the toddler ages in which spontanous recovery is observed (1,4). Our patient did not have such a history and her echocardiography was normal. It's interesting that she had a sibling who died at the age of 2 months because of heart failure, which could be related to Alström syndrome.

We are not sure whether our patient has hypogonadism or polycystic ovary syndrome (PCOS) because she is prepubertal yet. Evaluation will be considered during her puberty. Her hyperinsulinism makes us think that she has a high risk of having PCOS. She is a candidate for metformine therapy for her hyperinsulinism (13).

In Alström syndrome; broncial asthma has been defined in only a few patients (4). Asthma in our patient does not have an allergic origin but is certainly an additional association of Alström syndrome.

Conlusion

Alström syndrome should be kept in mind in patients with mental retardation, obesity, hypogonadism, visual and renal signs which are misdiagnosed as having Bardet-Biedl syndrome. A diagnosis of Alström syndrome should be considered in infantile cone and rod retinal dystrophy. Particularly if the weight is above 90th percentile or if there is an infantile cardiomyopathy.

Alström syndrome is one of the syndromic reasons of Type 2 diabetes mellitus of childhood and should be kept in mind, in these kind of the patients.

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ACUTE DISSEMINATED ENCEPHALOMYELITIS ASSOCIATED WITH EPSTEIN-BARR VIRUS INFECTION

Ergin Çiftçi* ✣ Erdal İnce* ✣ Tuğba Belgemen* ✣ Suat Fitöz** ✣ Gülhis Deda* Ülker Doğru*

SUMMARY

Acute disseminated encephalomyelitis (ADEM) is a presumed immune-mediated, demyelinating disease of the central nervous system. Many infections and vaccinations have been reported to be associated with ADEM. In this report, we present a girl with ADEM associated with Epstein-Barr virus infection. She was treated with methylprednisolone and exhibited complete clinical and radiological improvement.

Key Words: Acute Disseminated Encephalomyelitis, Epstein-Barr Virus, Methylprednisolone

ÖZET

Epstein-Barr Virus Enfeksiyonu İle İlişkili Akut Dissemine Ensefalomiyelit

Akut dissemine ensefalomiyelit (ADEM), santral sinir sisteminin immün aracılı olduğu var sayılan demiyelinizan bir hastalığıdır. ADEM ile çok sayıda enfeksiyon ve aşılama arasında bağlantı kurulmuştur. Bu bildiride Epstein-Barr virus enfeksiyonuna bağlı akut dissemine ensefalomiyelit gelişen bir kız hasta sunulmuştur. Hasta metilprednisolon ile tedavi edilmiş ve tam klinik ve radyolojik iyileşme göstermiştir.

Anahtar Kelimeler: Akut Dissemine Ensefalomiyelit, Epstein-Barr Virus, Metilprednisolon

Acute disseminated encephalomyelitis (ADEM) is an acute inflammatory demyelinating disorder of the central nervous system commonly seen in children and young adults (1). With modern imaging techniques ADEM is now readily and more commonly diagnosed. Magnetic resonance imaging (MRI) of cases with ADEM typically reveals asymmetrical, bilateral T2 hyperintense lesions in white matter and deep gray matter (2). Although the pathogenesis of ADEM is yet not well known, histologically and clinically, it resembles experimental autoimmune encephalomyelitis (3, 4). Therefore, it is possibly related to an inappropriate autoimmune reaction to myelin antigens of the host triggered by an exogenous antigen.

The disease is clinically characterized by the acute onset of neurological symptoms including alternation of consciousness, paresis, ataxia, seizures, behavioral changes, and urinary incontinence after an infection or immunization (1, 5, 6). Although various viral and bacterial pathogens have been associated with ADEM, the preceding infection cannot be identified frequently (1, 5, 6), and ADEM after Epstein-Barr virus infection has only rarely been reported in English literature (7-11). In this report, we present a girl with ADEM associated with Epstein-Barr virus infection.

Case Report

A 4-year-old girl was admitted to our hospital with a 7-day history of fever, sore throat, headache, and drowsiness noticed in last 2 days. She was well until three days prior to admission when her complaints had appeared abruptly. She had no recent history of vaccination. She was

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examined by her pediatrician in the first day of her disease, during this visit, the diagnosis of exudative tonsillitis was established and the treatment of cefuroxime axetil was initiated without throat culture or rapid antigen detection for group A streptococcus. Despite excellent compliance to the treatment, her complaints persisted until her admission.

On the admission, the child was conscious, body temperature was 38.3ºC. Pharyngeal examination revealed severe inflammation, swelling and exudate in tonsillar area. Enlarged, tender lymph nodes were noted in cervical, and inguinal regions. The liver and spleen were palpable 2 and 3 cm below the costal margins, respectively. Neurological examination was completely normal.

Laboratory examinations included hemoglobin level of 12.5 g/dl, leukocyte count of 25,100/mm^3 (24% neutrophils, 50% lymphocytes, 24% atypical lymphocytes, and %2 monocytes), and platelet count of 623,000/mm^3. Sedimentation rate was 70 mm/h and C-reactive protein level was 0.26 mg/dl. Blood chemistry and anti-streptolysin O titer were within normal limits. Cranial computed tomography scan was normal. Cerebrospinal fluid (CSF) examination was normal except for slightly lymphocytic pleocytosis (40 lymphocytes/mm^3). There was no serologic evidence of acute infection by measles, rubella, mumps, cytomegalovirus, human immunodeficiency virus, herpes simplex virus type I and II, varicella-zoster, hepatitis A, B, and C viruses, Toxoplasma gondii, or Mycoplasma pneumoniae, while Epstein-Barr virus viral capsid antigen IgM and IgG were positive. The diagnosis of infectious mononucleosis was established, cefuroxime treatment was discontinued, and patient was followed symptomatically.

Patient's fever returned to normal at the second day of hospitalization. Tonsillitis, enlarged lymph nodes, and hepatoslenomegaly were also begun to regress spontaneously. On the fourth day of hospitalization, however, the patient was not able to walk and she had expressive dysphasia. The physical examination revealed hyperactive deep tendon reflexes, generalized muscle rigidity, bilaterally positive Achilles' clonus and Babinsky's sign. Repeated CSF examination was completely normal, and CSF oligoclonal band was negative. Cranial MR imaging revealed increased signal intensity in areas of lentiform nucleus, caudate nucleus, and frontal, parietal, and temporal subcortical white matter (Figure 1). The lesions were hypo- or izointense on T1-weighted images and did not show any contrast enhancement after intravenous gadolinium injection.

According to the findings on MRI, the diagnosis of ADEM was established, and the treatment with methylprednisolone (20 mg/kg/day, intravenously for three days, then 2 mg/kg/day, orally for ten days) was initiated. Her abnormal neurological findings were improved on the second day, and completely resolved at the end of the treatment. Control MRI performed on the seventh day of the treatment revealed significant regression of the ADEM lesions, and patient was discharged after the discontinuation of methylprednisolone therapy.

Control MR examination after 3 months demonstrated complete resolution of the lesions (Figure 2). No recurrence was observed during 18 months of follow-up.

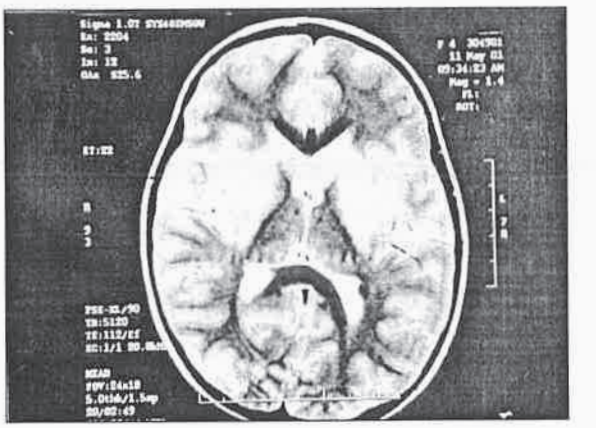

Figure 1: Axial T2-weighted image shows bilateral symmetrical hyperintense lesions involving the lentiform and caudate nucleus.

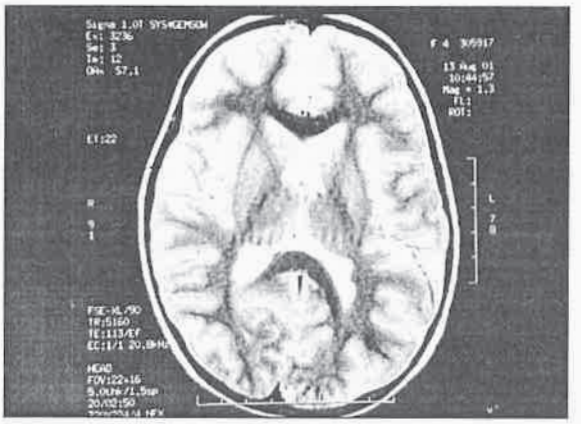

Figure 2: Axial T2-weighted image obtained 3 months later reveals complete regression of the lesions.

Discussion

ADEM is thought to be an autoimmune disease precipitated by infectious agents, which trigger an autoimmune reaction against neural constituents with cross-reactive molecular structures (5, 6). Histologically, multifocal perivenous infiltrations with lymphocytes and plasma cells are seen with edema and demyelination (5, 6). The triggering factors for ADEM include viral illnesses such as measles, rubella, mumps, herpes simplex, chickenpox, cytomegalovirus, and coxsackie B, vaccines such as rabies, pertussis, diphtheria, tetanus, smallpox, influenza, Japanese B encephalitis, mumps/measles/rubella, group A and C meningococcus, bacteria such as Streptococcus pyogenes, Mycoplasma pneumoniae and Salmonella, and drugs such as sulphonamides and para-aminosalicyclic acid (5, 6).

Our patient did not have any recent immunization history, and we could not demonstrate evidence of acute viral or bacterial infection other than Epstein-Barr virus infection. She had clinical findings consistent with infectious mononucleosis and acute Epstein-Barr virus infection was confirmed by specific antibodies. Many uncommon and unusual conditions including aseptic meningitis, encephalitis, transverse myelitis, cranial nerve paralyses, ataxia, seizures, Alice in Wonderland syndrome, and Guillain-Barré syndrome have been reported to be associated with Epstein-Barr virus infection (7, 12), however, ADEM has only rarely been reported (7-11).

After an infection or vaccination, ADEM presents as an acute or subacute illness. Fever, headache, and meningeal irritation sings are the most common initial symptoms and findings followed by neurological findings such as seizures, focal neurological deficits, and altered consciousness. CSF abnormalities in patients with ADEM often include a modestly elevated protein level, and occasionally some degree of pleocytosis. CSF oligoclonal bands may be seen on presentation but do not persist later (5, 6)· The electroencephalography usually shows slow wave activity. The cranial computed tomography (CT) is usually normal. MRI is usually required to establish the diagnosis (5, 6). The cranial CT of our patient was normal, while MRI revealed brain involvement typical for ADEM. She also had some vague symptoms such as headache and drowsiness possibly associated with ADEM at the time of cranial CT examination performed on admission. Although the CT scan and MRI were not performed simultaneously, this observation supports the opinion that MRI is required for the diagnosis of ADEM.

ADEM is mostly confused with multiple sclerosis. On the contrary of multiple sclerosis, ADEM follows a monophasic clinical course, and generally occurs in children (5, 6). We have not observed a recurrence during 18 moths of follow-up in our patient.

Treatment of ADEM has not been systematically studied, and spontaneous improvement has been noted. Except for its fulminant form, the acute hemorrhagic necrotizing encephalomyelitis (Hurst syndrome), the prognosis of ADEM has been uniformly reported as favorable (5, 6). Treatment of patients with ADEM has focused on a presumed autoimmune etiology. The use of corticosteroids in the treatment of ADEM is based on their efficacy in preventing or modifying the course of experimental allergic encephalomyelitis and their use in treating MS (5, 6). Oral and IV steroids are often effective, and represent the most widely

used treatment (5, 6), although they have been reported to be successful in most patients with ADEM, relapses have also been reported (13). We obtained excellent response with high-dose intravenous methyl-prednisolone therapy, and continued oral therapy for another 10 days. Intravenous immunoglobulin, plasmapheresis, and cytostatic drugs are alternative treatment options in patients who do not respond to steroid therapy (14-16).

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A CASE OF IDIOPATHIC PULMONARY HEMOSIDEROSIS PRESENTING WITH PULMONARY HEMORRHAGE DURING EPSTEIN-BARR VIRUS INFECTION

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SUMMARY

Pulmonary hemorrhage, a rare and life-threatening event in children, results from various disorders. Idiopathic pulmonary hemosiderosis characterized by repeated episodes of pulmonary hemorrhages is a rare disease with unknown etiology. It has also been reported that pulmonary hemorrhage may be seen during Epstein-Barr virus infection. In this report we present 2 year-old-girl complained with respiratory distress, pallor, fever and sore throat. She diagnosed Epstein-Barr virus infection, anemia and pneumonia. Because she had anemia and respiratory distress simultaneously, we highly suspected from pulmonary hemorrhage. But hemosiderin-laden macrophages were not demonstrated in gastric aspirates. The girl treated symptomatically and healed uneventfully. After one uneventfully year, she was admitted with pallor and respiratory distress, and pulmonary hemorrhage was demonstrated on lung biopsy. The diagnosis of idiopathic pulmonary hemosiderosis was established. Three other pulmonary hemorrhage attacks were observed at the follow-up. We suggest that Epstein-Barr virus infection might be one of the possible factors responsible from idiopathic pulmonary hemosiderosis.

Key Words: *Epstein-Barr Virus, Pulmonary Hemorrhage, Idiopathic Pulmonary Hemosiderosis*

ÖZET

Epstein-Barr Virus Enfeksiyonu Sırasında Akciğer Kanaması ile Ortaya Çıkan İdiopatik Pulmoner Hemosiderosis Olgusu

Çocuklarda ender ve hayatı tehdit eden bir durum olan akciğer kanaması çeşitli bozukluklar sonucunda oluşur. Yineleyen akciğer kanaması atakları ile karakterize olan idiopatik pulmoner hemosiderosis etiolojisi bilinmeyen ender bir hastalıktır. Epstein-Barr virus enfeksiyonu sırasında da pulmoner kanama görülebildiği bildirilmiştir. Bu bildiride solunum sıkıntısı, solukluk, ateş ve boğaz ağrısından yakınan 2 yaşında bir kız hasta sunulmuştur. Hasta Epstein-Barr virus enfeksiyonu, anemi ve pnömoni tanısı almıştır. Eşzamanlı olarak anemisi ve solunum sıkıntısı olması nedeniyle kuvvetle akciğer kanamasından şüphe edilmiştir. Ancak mide suyunda hemosiderin-yüklü makrofaj gösterilememiştir. Hasta semptomatik olarak tedavi edilmiş ve sorunsuz olarak iyileşmiştir. Bir yıl sonra hasta solukluk ve solunum sıkıntısı ile başvurmuş ve akciğer biyopsisinde akciğer kanaması gösterilmiştir. İdiopatik pulmoner hemosiderosis tanısı konulmuştur. İzlemde üç akciğer kanaması atağı daha gözlenmiştir. Epstein-Barr virus enfeksiyonunun idiopatik pulmoner hemosiderosisden sorumlu olası faktörlerden biri olabileceği kanısına varılmıştır.

Anahtar Kelimeler: *Epstein-Barr Virus, Pulmoner Kanama, İdiopatik Pulmoner Hemosiderosis*

Pulmonary hemorrhage in children is rare but can be life threatening. Infections, trauma and foreign bodies are probably the most common causes of pulmonary hemorrhage in children. However, pulmonary hemorrhage results from various disorders such as cardiovascular, toxic, neoplastic, vasculitic, and idiopathic (1). We recently treated a 2 year-old-girl who had pulmonary hemorrhage during Epstein-Barr virus infection. Because bleeding diathesis including pulmonary hemorrhage has been reported in Epstein-Barr virus infection (2, 3), it was also

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possible that her pulmonary hemorrhage was related to Epstein-Barr virus infection. However, she experienced other pulmonary hemorrhage attacks at the follow-up, and the diagnosis of idiopathic pulmonary hemosiderosis was established. To our knowledge, this is the first article reported a case of idiopathic pulmonary hemosiderosis presenting with pulmonary hemorrhage during Epstein-Barr virus infection.

Case Report

A 2-year-old girl was admitted to our hospital with a 3-day history of fever, sore throat, cough, dyspnea, and pallor. She was well until three days prior to admission when her complaints had appeared abruptly. She was being followed by a pediatrician regularly, and her physical examination and complete blood count was uneventful during the last visit performed one month ago.

On admission, the child had severe dyspnea and pallor. Her breathing rate was 60/min; there were retractions in intercostal, subcostal and suprasternal regions. Her breath sounds were decreased especially in the right hemithorax. Her body temperature was 38.3°C. Pharyngeal examination revealed severe inflammation, swelling and exudate in tonsillar area. Enlarged, tender lymph nodes were noted in cervical, axillary, and inguinal regions. The liver and spleen were palpable 4 and 5 cm from the costal margins, respectively. Her transcutaneous oxygen saturation was 94% while receiving 6-l/min nasal oxygen.

Laboratory examinations included hemoglobin level of 5.2 g/dl, leucocyte count of 17.300/mm^3 (20% neutrophils, 54% lymphocytes, 24% atypical lymphocytes, and % 2 monocytes), and platelet count of 318.000/mm^3. Sedimentation rate was 26 mm/h and C-reactive protein level was 0.58 mg/dl. Blood chemistry was normal except for slightly elevated transaminases (ALT; 65 U/L, AST; 50 U/L, normal range <35 U/L). Chest X-ray examination showed bilateral perihilar consolidation (Figure 1). Epstein-Barr virus viral capsid antigen IgM and IgG were positive. The diagnosis of infectious mononucleosis related to Epstein-Barr virus infection, pneumonia and anemia was established. Intravenous fluid and nasal oxygen therapy were started.

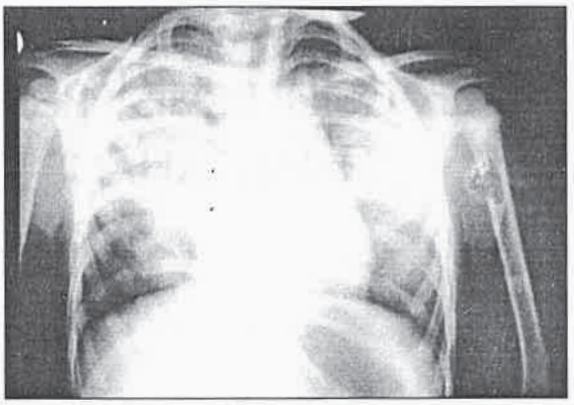

Figure 1: Bilateral perihilar consolidation is shown in the X-ray graphy of the thorax. Apex and basal areas are partially conservated.

On the second day of hospitalization, respiratory distress of the patient increased and her hemoglobin value decreased to 4.7 g/dl. After blood was taken for laboratory investigations, she was transfused with concentrated erythrocytes and her hemoglobin value increased to 9.3 g/dl. According to the results obtained from pretransfusion blood specimens; MCV: 71 fl, MCH: 22 pg, MCHC: 31 gr/dl and RDW: 16.7. Reticulocyte count was 2.3%. Serum bilirubin values were normal. Direct Coombs test was negative. The hemoglobin electrophoresis was normal. Investigation of stool for blood was negative. Coagulation tests were within normal limits. Serum iron profile was consistent with iron deficiency (serum iron: 28 mg/dl, unsaturated iron binding capacity: 480 mg/dl, transferrin saturation: 5.5%), while serum ferritin and serum haptoglobulin were normal. Bone marrow aspiration was normal.

On the fourth day of hospitalization, her respiratory status deteriorated and concomitantly her hemoglobin value decreased to 4.8 g/dl. She was transfused with concentrated erythrocytes

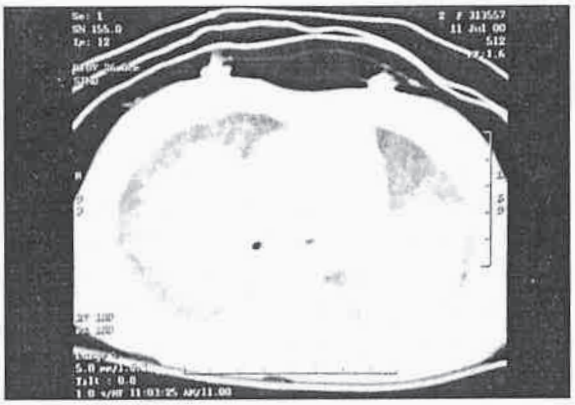

Figure 2: Bilateral perihilar consolidation is shown in the computed tomography of the thorax.

again and her hemoglobin value increased to 12.9 g/dl. A computed tomography scan of the thorax revealed bilateral perihilar consolidation (Figure 2). Because of poor condition of the patient, teicoplanin and meropenem were started. Reticulocyte counts, serum bilirubin values, direct Coombs test, and investigation of stool and urine for blood, serum haptoglobulin, and coagulation tests remained within normal limits. A broad viral serology panel was negative except for Epstein-Barr virus. Serology for antinuclear, anti double stranded DNA, antinuclear cytoplasmic, and antiglomerular basement membrane antibodies were negative. No pathogens were isolated from throat swab and blood specimens. Tuberculin skin test was negative and acidoresistant bacteria were not found in gastric aspirates. Otolaryngorhinological examination did not reveal a bleeding focus.

Since patient's dyspnea did not respond to the antimicrobial therapy teicoplanin and meropenem were discontinued in the seventh day of treatment. On the fifteenth day of hospitalization while receiving supportive care, patient's breathing difficulty had decreased. During that time her hemoglobin value had stayed between 9.4-10 g/dl, and her hepatosplenomegaly and lymphadenopaties had resolved. Because of the unexplained abrupt decrease in hemoglobin value and the concomitant increase in breathing difficulty we considered the possibility of pulmonary hemorrhage or pulmonary hemosiderosis. Radionuclide scan performed on the twentieth day of hospitalization showed no active pulmonary hemorrhage. Repeated computed tomography scan of the thorax revealed decrease in perihilar consolidation (Figures 3 and 4). Hemosiderin-laden macrophages were not demonstrated in gastric aspirates. The girl treated symptomatically and healed uneventfully. After twenty-two days of hospitalization, she was discharged from the hospital. Although evaluation for milk-protein allergy was negative we offered milk-free diet.

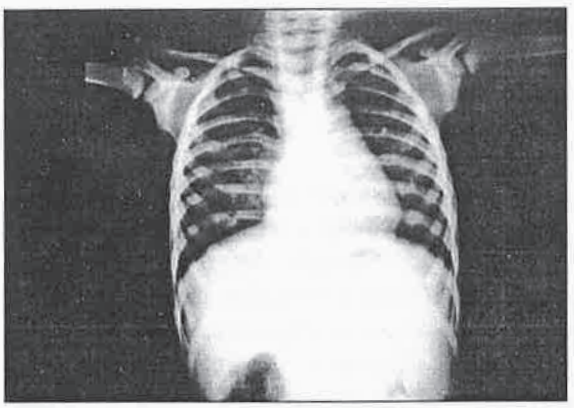

Figure 3: Two weeks later, partially resolution is seen in perihilar consolidation.

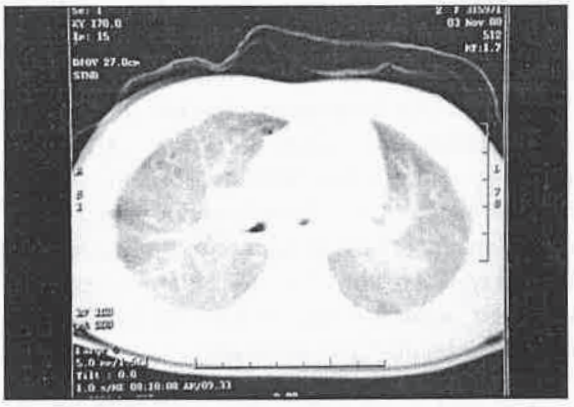

Figure 4: In computed tomography of the thorax performed two weeks later, complete resolution is seen in perihilar consolidation.

After one uneventfully year, she admitted with complaints of cough, dyspnea, hemoptysis and pallor. She had tachypnea, retractions, and bilateral diminished breathing sounds. Her hemoglobin level was 5 g/dl. She did not have any physical and laboratory finding concordant with Epstein-Barr virus infection. A computed tomography scan of the thorax revealed bilateral perihilar consolidation. She was transfused with concentrated erythrocytes and her hemoglobin value increased to 9.8 g/dl. After written consent from her family, an open lung biopsy was performed. Microscopically, typical features of idiopathic pulmonary hemosiderosis were seen including recent intra-alveolar hemorrhage, large numbers of intra-alveolar hemosiderin-laden macrophages, and mild diffuse interstitial fibrosis. The diagnosis of idiopathic pulmonary hemosiderosis was established. Although she received inhaled corticosteroid therapy, three similar attacks were observed.

Discussion

Infectious mononucleosis, which is the most commonly caused by Epstein-Barr virus infection, is manifested typically by fever, exudative pharyngitis, lymphadenopathy, hepatosplenomegaly, and atypical mononucleosis (4). The spectrum of disease is variable, ranging from asymptomatic to fatal infection. Bleeding is a rare complication of infectious mononucleosis and manifested by various clinical pictures. Pulmonary hemorrhage (2, 3), tonsillar hemorrhage (5), hematuria (6), retinal hemorrhage (7), subarachnoid hemorrhage (8), cerebral hemorrhage (9), and subcapsular splenic hematoma (10) have been reported in patients with Epstein-Barr virus infection. Although bleeding diathesis has been ascribed to various factors such as thrombocytopenia (11), coagulopathy related to hepatic dysfunction (12), vessel wall erosion (5), and friability of the enlarged spleen (10), exact mechanism of bleeding remains obscure in some cases.

Our patient had Epstein-Barr virus infection in the first pulmonary hemorrhage attack proved by computed tomography scans of thorax. If we had performed a radionuclide scan or bronchoscopy in the acute period, pulmonary hemorrhage could have been demonstrated. In the first attack we could not explain why pulmonary hemorrhage occurred. She did not have thrombocytopenia, and her coagulation tests including bleeding time were normal. Her pulmonary hemorrhage might have been caused by changes in vascular integrity as speculated by Weinstein and O'Hare (3). However, pulmonary hemorrhage attacks recurred in our patient and the diagnosis of idiopathic pulmonary hemosiderosis was established.

Idiopathic pulmonary hemosiderosis is a rare disease, predominantly occurring in children and young adults, with a markedly variable clinical course characterized by repeated episodes of multifocal pulmonary hemorrhages. The condition occurs in the absence of primary cardiac disease, glomerulonephritis, or other disorders associated with intrapulmonary bleeding. Idiopathic pulmonary hemosiderosis is defined clinically by the triad of hemoptysis, diffuse pulmonary infiltrates on the chest roentgenogram, and iron deficiency anemia. Despite numerous experimental morphologic, immunologic, and ultrastructural studies, the etiology and pathogenesis of idiopathic pulmonary hemosiderosis are not known (13).

Based on evidence obtained from our patient and the other cases in literature, we suggest that pulmonary hemorrhage may be a potential complication in Epstein-Barr virus infection. However, pulmonary bleeding may result from various factors other than Epstein-Barr virus infection. For this reason, patients with Epstein-Barr virus infection associated with pulmonary hemorrhage must be followed for other possible causes such as idiopathic pulmonary hemosiderosis. Furthermore, it is an attractive assumption that Epstein-Barr virus infection may be one of the several possible factors for the development of idiopathic pulmonary hemosiderosis.

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FIBROEPITHELIAL POLYP OF THE URETER IN A YOUNG ADULT

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SUMMARY

We report a case of primary fibroepithelial polyp of the left ureter. The patient was a 20-year-old-girl. During ureteroureterostomy a fibroepithelial polyp in the left ureter was found and resection of the polyp from the left ureter and a partial ureterectomy with an end-to-end anastomosis was performed.

Key Words: *Fibroepithelial Polyp, Üreter, Ureteroureterostomy*

ÖZET

Genç Erişkinde Görülen Üreteral Fibroepitelyal Polip

Sol üreterinde primer fibroepitelyal polip tespit ettiğimiz bir vakayı sunuyoruz. Hasta 20 yaşında bir bayan idi. Ureteroureterostomi sırasında sol üreterde fibroepitelyal polip bulundu ve sapıyla birlikte rezeke edildi. Daha sonra parsiyel üreteroktomi ve uç uça anastomoz gerçekleştirildi.

Anahtar Kelimeler: *Fibroepitelyal Polip, Üreter, Üreteroüreterostomi*

Fibroepithelial polyp is a benign neoplasm of a mesodermal origin that arises in the wall of the ureter, renal pelvis, bladder or urethra[1]. Here we report a case of a fibroepithelial polyp of the ureter in a young adult.

Case Report

A 20-year-old girl was admitted to another institution with gross painless hematuria. Her physical examination was within normal limits. Abdominal ultrasound examination demonstrated an echogenic structure with polypoid projections extended into the bladder suggesting bladder tumor (Figure-1). The patient was then referred for cystoscopy to our institution. At cystoscopy a papillary tumor was seen protruding from the left ureteral orifice. An intravenous pyelogram confirmed the above finding and revealed a large obstructing filling defect located in the distal third of the left ureter. Rigid ureterorenoscopy was then undertaken to obtain tissue sample for pathological examination. Ureterorenoscopy of this lesion revealed a polypoid ureteral lesion starting from the distal third of the left ureter and protruding into the bladder, a biopsy of which was done and the remainder protruding part was excised. Pathologic examination of the tissue specimen confirmed a fibroepithelial polyp.

Then the patient lost follow-up. After admitted 5 months later, she underwent an uneventful left ureterotomy and an 8 cm fibroepithelial polyp that stemmed from a single stalk was excised (Figure-2) and a partial ureterectomy with an end-to-end anastomosis was performed. A double-J stent was placed at the end of the procedure and removed 2 months postoperatively. At follow-up, the patient was asymptomatic and had no

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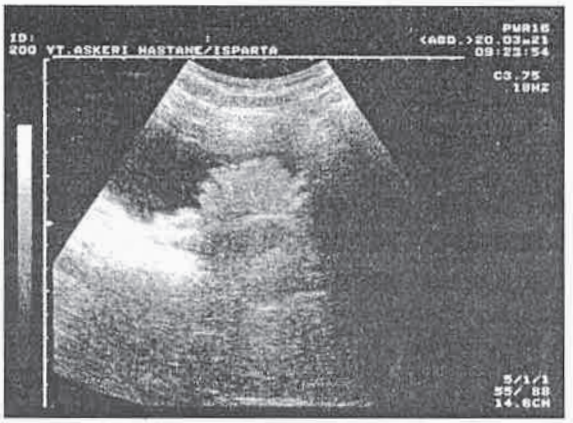

Figure 1: Preoperative USG showing a tumor projecting into bladder lumen

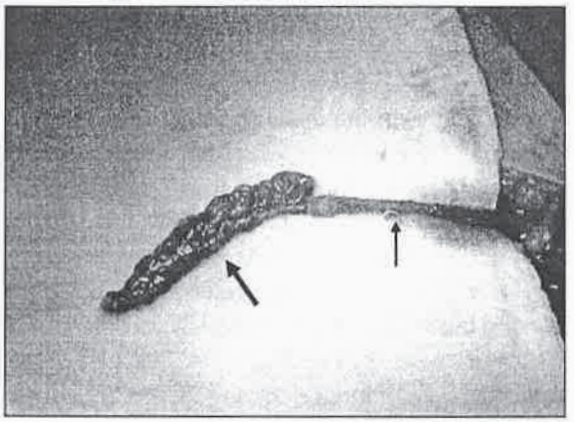

Figure 2: Intraoperative photograph of left ureter showing single strand of 8 cm polyp Thin arrow showing left ureter and thick arrow showing fibroepithelial polyp

evidence of disease on cystoscopy and IVP for one year.

Discussion

Ureteral fibroepithelial polyps are rare neoplasms(1). These lesions can occur at any age and has been reported even in a neonate(2). Most patients present with hematuria and/or flank pain(1). Ureteral fibroepithelial polyps are usually located in the proximal third of the ureter(1). In our case the polyp was in the distal third of the ureter.

Radiologic appearance is variable according to the gross appearance of the tumor. Intravenous urography may show an intraluminal lesion that is smooth or polypoid and does not cause marked dilatation of the urinary tract. If identification cannot be made by intravenous urography, retrograde and/or antegrade pyelography should be made(3). Preoperative radiologic examination was important in this patient because it directed the proper mode of therapy. Ureteroscopy can differentiate clearly the smooth, regular surface of pedunculated fibroepithelial polyps from the irregular, friable appearance of urethelial carcinoma(4). Appropiate treatment of these tumors is by local excision with or without segmental resection(5).

In our case, the polyp was removed completely with its stalk so that an obstructing base would not be left. Recurrences have not been reported in spite of observations of up to 15 years(3). Although our follow-up is minimal (one year), no recurrence is noted.

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