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COMPARISON OF FIBER DIAMETER DISTRIBUTIONS DEDUCED BY MODELLING COMPOUND ACTION POTENTIALS RECORDED BY EXTRACELLULAR AND SUCTION TECHNIQUES*

Nizamettin Dalkılıç** • Ferit Pehlivan**

SUMMARY

In this study, the extracellular and suction techniques, used widely to record compound action potentials (CAP), are compared in respect to their ability to deduce fiber diameter distribution (FDD). Fiber diameter distribution derived by applying the deconvolution model to CAP depends not only on the modelling but also on the recording techniques. The FDDs determined by these two techniques were compared with that predicted by histologic means.

In our model study, a waveform for single fiber action potential (SFAP) is defined as $f(t)=A\sin(t/\tau_1).\exp(-t/\tau_2)$ *where the parameters* t_1 *and* t_2 *were taken from the literature and given for the SFAP of each fiber diameter between d=3-22 μm, and A was chosen to normalise the amplitude of SFAP to one.*

We substituted the measured CAPs in to our model and calculated the histograms related with the fiber diameter distribution of the sciatic nerve trunk. We saw that the FDD as predicted from the CAP, recorded by the extracellular techniques, coincides better with that of the histologically determined FDD than that predicted by suction techniques.

Key words: *Compound action potential, conduction velocity distributions, extracellular techniques, suction techniques, sciatic nerve*

ÖZET

Ekstraselüler ve "Suction" Teknikleri ile Kaydedilen Bileşik Aksiyon Potansiyellerinden Model ile Elde Edilen Lif Dağılım Histogramlarının Karşılaştırılması

Bu çalışmada, bileşik aksiyon potansiyeli (BAP) gözlenmesinde sıkça kullanılan ekstraselüler ve "suction" teknikleri, lif dağılım histogramı (LDH)nın belirlenmesindeki üstünlükleri bakımından karşılaştırılmıştır. Dekonvolüsyon modelinin BAP'a uygulanmasıyla elde edilen LDH'ı, model ile birlikte kayıt yöntemine de sıkıca bağlıdır. Ekstraselüler ve "suction" kayıtlarına model uygulanmasıyla elde edilen LDH'lar histolojik LDH'lar ile karşılaştırılmıştır.

Model çalışmasında tek lif aksiyon potansiyeli (TLAP) için $f(t)=A\sin(t/\tau_1).\exp(-t/\tau_2)$ *şeklinde bir fonksiyon önerilmiştir. Bu fonksiyona ait parametrelerden* t_1 *ve* t_2 *lif çapının d=3-22 μm arasındaki değerleri için literatürden TLAP süreleri dikkate alınarak, A ise TLAP genlikleri 1'e normalize edilerek belirlenmiştir.*

Ekstraselüler BAP kayıtlarından elde edilen LDH'ların, "suction" kayıtlarından elde edilen LDH'lara göre, histolojik LDH ler ile daha iyi uyum içinde oldukları görülmüştür.

Anahtar Kelimeler: *Bileşik aksiyon potansiyeli, iletim hız dağılımı, ekstraselüler tekniği, suction tekniği, siyatik siniri*

Compound action potential (CAP) recorded from a nerve trunk contains information concerning the number of active fibers and the propagation velocities of their action potentials. For the functional investigation of nerves in situ, the CAP has found widespread application in basic research and, in particular, for the assessment of neuromuscular disease (1,2).

Many clinical branches such as neurology, orthopaedics and physical medicine rely in part on the electrophysiological properties of nerves for characterising the peripheral nerve function in health and disease. One of the commonly used measures of nerve function is the conduction velocity distribution of the nerve bundle (3,4). But the measured distribution depends deeply on the recording techniques and on the physical model chosen for the calculations.

There are two widely used recording techniques for determining the function of isolated nerve trunks; extracellular and suction techniques (5,6,7). Both techniques have their advantages and disadvantages. In this study, recording, analysing, and modelling have been carried out in order to compare the success of these techniques. A model has been proposed to compare the conduction velocity distribution of a nerve

* This study greatly depends on the PhD. thesis made in Department of Biophysics.

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trunk from CAPs recorded by suction and by extracellular techniques.

Model studies on which the calculations of the velocity distribution depends involve two types of problems, so called "the forward problem" and "the inverse problem", which complement to each other.

The Forward Problem: By defining a waveform function for a single fiber action potential (SFAP) for each group of the nerve fibers, and also considering the time delay of each group of fibers to different recording distances, it is assumed that the CAP is a weighted sum of delayed SFAPs (8,9,10,11).

A widely used simplification for the SFAP in CAP modelling is to postulate a fixed "standard" SFAP waveform $f_o(t)$. The amplitude and duration of SFAP waveforms are varied as a function of propagation velocity. Assuming SFAP duration scaled by a power of the propagation velocity, the waveform of $f_o(t)$ can be expressed as

$$f(t;v)=A(v)\, f_o(v^q t) \qquad (1)$$

where A(v) is the variation in the amplitude of SFAP with velocity v (9). Many authors have adopted an empirical relationship related with the dependence of the SFAP waveform on propagation velocity of the form

$$A(v)=d^p \qquad (2)$$

where d is the fiber diameter and p is a constant (9,12).

In order to establish the model of CAP, based on the underlying SFAP and on the propagation velocity characteristics of the fiber population, a set of assumptions must be required;

a) The CAP can be represented as a linear superposition of its constituting elements, the SFAPs.
b) Action potentials propagate independently along different fibers.
c) All fibers contributing to the CAP are activated simultaneously and instantaneously upon electrical stimulation.
d) All fibers contributing to the CAP are activated at the same position along the nerve. The distance actually propagated by each individual spike is equal.
e) The propagation velocity of the action potential between stimulation and recording electrode is constant.

Based on the above assumptions, a mathematical statement of CAP may be expressed as

$$CAP(t) = \sum_{i=1}^{N} w_i f_i(t - \tau_i) \qquad (3)$$

where CAP(t): the observed compound action potential as a function of time; N: the number of fiber classes; w_i: the amplitude-weighting coefficients for class i; $f_i(t)$: the SFAP for conduction velocity (cv) for class i; τ_i :the propagation delay for fibers in class i (8,13).

The weighting coefficients (w_i) are general parameters to account for all influences on the contribution of each fiber class to the observed CAP. Since the amplitude of the SFAP may vary from class to class, w_i has a factor $A(v_i)$ to account for this dependence. The contribution of the fibers in class i to the CAP will also be influenced by the number of fibers in the class (m_i); this dependence is denoted $H(m_i)$. Thus w_i may be expressed as

$$w_i = A(v_i).H(m_i) \qquad (4)$$

where m_i: the number of fibers activated in class i; $A(v_i)$: SFAP amplitude dependence on conduction velocity; $H(m_i)$: functional dependence of the weighting coefficients on the number of fibers in cv class i (8,13).

The CAP model of equation (3) can be formulated in terms of discrete time by using equally spaced samples for the SFAP and CAP function. Assuming that there are K values of the CAP for the k'th discrete (equally spaced) time point, the discrete values of observed $CAP(t_k)$ depending on linear combination of single constituents from each conduction velocity class, is

$$CAP(t_k) = \sum_{i=1}^{N} w_i f_i(t - \tau_i) \qquad k=1,2.....K \qquad (5)$$

or

$$CAP(t_k) = \sum_{i=1}^{N} A(v_i)H(m_i)f_i(t_k - \tau_i) \qquad (6)$$

The Inverse Problem: This is a mathematical procedure for estimating the propagation velocity distribution of the fibre population in a nerve from recorded CAPs. The problem can be solved by the inverse mathematical procedure as we followed to construct the CAP from SFAPs, that is, to find the weighting coefficients (w_i) in terms of recorded CAP.

MATERIALS AND METHODS

Experiments were performed to record the CAP from isolated frog sciatic nerve by extracellular and suction techniques. The frogs were dissected approximately one hour before the experiments were started.

During the dissection, frog Ringer's solution was used to keep the nerve moist. One end of the dissected nerve was tied with threads and the nerve was transferred into the bathing system of the suction technique. The distal end of the bundle was drawn snugly into the barrel of a saline-filled glass pipette whose tip is thin enough to get the nerve in it by the application of suction to the free end of the capillary (suction electrode). The suction pipette is connected to a differential amplifier.

The other tied end of the nerve was placed on the stimulating electrode positioned at the upper side of the bath, but not in touch with the Ringer's solution.

When the nerve was stimulated by a supramaximal electrical pulse, the action potentials were recorded using the pre-amplifier (Harvard Isolated Preamplifier), that had a high input impedance. The CAP signals were digitised with a 0.04 ms sampling period by an A/D converter (PCL 812PG) and 512 time samples for a CAP record were stored on a hard disk.

After completing the suction record, the nerve was moved to the extracellular moist chamber from suction chamber. Stimulating the distal end of the bundle, the same experimental procedure that we had followed for the suction record was used to record the extracellular CAP from the same nerve bundle.

Model Studies for Determining the Conduction Velocity Distribution from the CAP Records: There are many models proposed for constructing the conduction velocity distribution in a nerve by analysing the CAPs (11,14,15). Each model has advantages and disadvantages as compared with the others. In our model studies, we introduce first a function to simulate the single fiber action potential (SFAPs) by assuming it is relevant for each nerve fiber group.

In 1927, Gasser et al. assumed simply this function as a triangle (16). In those years, researchers thought that all fiber groups had the same SFAP waveshape, and so the triangle corresponding with this shape had a constant amplitude and duration. But it was later assumed that the duration of the SFAP should be different for each group, and then a relationship was proposed between the diameter of the fiber and the SFAP duration (8,17,18). It was also proposed that the amplitude of the SFAP should depend on the fiber diameter.

In this study, taking into account that a SFAP may possess two phases, we proposed a waveform function for the SFAP as

$$f(t) = A.\sin(t/\tau_{01}).\exp(-t/\tau_{02}) \quad (7)$$

where A, τ_{01} and τ_{01} are the parameters that mainly correspond to the amplitude, rising phase rate, and the total duration of a SFAP respectively.

The function f(t) that we suggested has two main advantages:

a) In most model studies, SFAP has been assumed as a triangle. A triangle has some sharp turnings, while our SFAP function deviates smoothly as we would expect naturally.

b) The function that we proposed has also a negative phase and it coincides with the negative phase seen in CAP recorded from frog sciatic nerve.

The parameter A was obtained by normalising the amplitude of the SFAP to one with any amplitude dependence of conduction velocity in to the weighting coefficients (w_i). The parameters τ_{01} and τ_{01} which are strongly related with the duration of SFAP are determined by following the procedure given below.

The temperature dependence of the conduction velocity-fiber diameter relation is given as the following form (19)

$$v = d(0.06T + 0.6) \quad (8)$$

has been used to calculate the conduction velocities of fibers having diameters between d=3 and 22 μm in 1 μm steps. Delay times for each fiber groups have also been calculated for the known travelling distances. Then the duration of SFAPs for selected fiber diameters has been determined from the SFAP duration-conduction velocity curves given in literature (17). All the results of these procedures are given in Table-1. Then, by using this table data, τ_{01} and τ_{01} parameters have been determined by curve fitting procedures. The results are given in the Table-2.

Analysis Procedure for the Inverse Problem: The normalised values of individual SFAP were sampled in 0.04 ms time interval and arranged in series according to and the delay times calculated for 2 cm travelling distance. Each series has duration of 5.36 ms which is long enough to cover the slowest SFAP. The series determined for each group has been put side by side in a spreadsheet application and a matrix of 20x135 dimensions for 20 group has been formed.

Since the CAP is a weighted sum of delayed SFAPs, the observed CAP can be written in a more compact matrix form

Table 1. Conduction velocities, SFAP durations and delay times for 2 cm recording distance for different fiber diameters. Conduction velocities were calculated according to the relation given by equation (9). SFAP duration was calculated according to the functional relation between the SFAP duration and fiber conduction velocities, proposed by Kovaks et al. (16).

Fiber diameter (d;μm)	Conduction velocity (m/s) (T=21 °C)	SFAP duration (ms)	Delay time (τ;ms) (for x=2 cm recording distance)
3	5,58	1,3	3,58
4	7,44	1	2,68
5	9,30	0,75	2,15
6	11,16	0,65	1,80
7	13,02	0,55	1,54
8	14,88	0,48	1,34
9	16,74	0,43	1,20
10	18,60	0,38	1,08
11	20,46	0,35	0,98
12	22,32	0,35	0,90
13	24,18	0,35	0,82
14	26,04	0,35	0,77
15	27,90	0,35	0,72
16	29,76	0,35	0,67
17	31,62	0,35	0,63
18	33,48	0,35	0,59
19	35,34	0,35	0,56
20	37,20	0,35	0,54
21	39,06	0,35	0,51
22	40,92	0,35	0,48

Table 2. The calculated values of A, to1, to2 which are defined in our SFAP function given by (7). A was calculated so as the amplitude of SFAP to be equal to 1 and, to1, to2 were calculated by taking into consideration SFAPs duration shown in Table-1.

Fiber diameter (d;μm)	Constant A	τ_{o2} (ms)	τ_{o2} (ms)
3	2.65	0.325	0.40
4	2.70	0.250	0.30
5	2.42	0.175	0.25
6	2.47	0.145	0.20
7	2.65	0.120	0.15
8	2.71	0.100	0.12
9	2.73	0.093	0.11
10	2.70	0.083	0.10
11	2.73	0.080	0.096
12	2.76	0.089	0.094
13	2.79	0.078	0.092
14	2.80	0.077	0.091
15	2.80	0.076	0.089
16	2.85	0.075	0.087
17	2.87	0.074	0.086
18	2.88	0.073	0.085
19	2.89	0.072	0.084
20	2.91	0.071	0.0835
21	2.92	0.071	0.083
22	2.94	0.071	0.082

$$CAP=A.w \tag{9}$$

where CAP=135X1 column vector composed of 135 time samples of the CAP $\{C(t_1), C(t_2),.....C(t_{135})\}$; A=135x20 matrix whose i'th column is the sampled SFAP function $f_i(t_k-d_i)$; w=20x1 column vector of the N weighting coefficients $\{w_1, w_2,.....w_{20}\}$.

In a matrix form, CAP(t) may be written in terms of A and w as,

$$\begin{bmatrix} CAP(t_1) \\ CAP(t_2) \\ CAP(t_3) \\ \vdots \\ CAP(t_{n-1}) \\ CAP(t_n) \end{bmatrix} = \begin{bmatrix} N_{11} & 0 & 0 & \cdots & 0 \\ N_{12} & N_{21} & 0 & \cdots & 0 \\ N_{13} & N_{22} & N_{31} & \cdots & 0 \\ \vdots & N_{23} & N_{32} & \cdots & 0 \\ & \vdots & N_{33} & & \vdots \\ N_{1n} & N_{2n} & \vdots & & \vdots \\ 0 & 0 & N_{3n} & & \vdots \\ \vdots & \vdots & 0 & & \vdots \\ \vdots & \vdots & \vdots & N_{201} & \\ \vdots & \vdots & \vdots & N_{202} & \\ \vdots & \vdots & \vdots & & \vdots \\ 0 & 0 & 0 & \cdots & N_{20n} \end{bmatrix} \begin{bmatrix} w_1 \\ w_2 \\ w_3 \\ \cdot \\ \cdot \\ \cdot \\ \cdot \\ \cdot \\ \cdot \\ \cdot \\ w_{19} \\ w_{20} \end{bmatrix}$$

In order to determine the conduction velocity distribution from the recorded CAPs and known SFAP properties, equation (9) may be viewed as a set of K equations having N unknowns. If the A has a form of square matrix (i.e., if K=N) and non-singular, then it would be possible in principle to solve equation (9) directly for the vector w.

It is a well known property of such systems that the least-squares solution for the vector w, may be obtained by remultiplying both sides of equation (9) by the transpose of the matrix A:

$$A^T.CAP(t)=A^T.A.w \tag{10}$$

In order to determine w, the below procedure was followed. Matrix A, bearing information about SFAP, was transferred from the spreadsheet into a mathematic software program which enable to matrix operations. Beginning after the pulse artifact,135 sampled values of the recorded CAP were also transferred into the same sheet in mathematic program. By solving the

matrix shown in equation (10), a series of values were found for w.

Above procedures have been performed for each extracellular and suction records of CAP(t) which are taken 2 cm apart from the stimulus site and so the weighting coefficients (w_i) have been determined for each five nerve

The weighting coefficients are general parameters to account for all influences on the contributions of each fiber classes to the observed CAP. Thus w_i may be expressed as

$w_i=A(v_i)H(m_i)$

where $A(v_i)$: SFAP amplitude dependence on cv; $H(m_i)$: functional dependence of the weighting coefficients on the number of fibers in class i (m_i: the number of fibers activated in class i).

To get a numerical fiber diameter distribution (H(m)), the relationship between the amplitude of SFAP and the fiber diameter should be known. The relationship is usually postulated as $A(d)=d^p$. Assuming p=1.6, we have obtained fiber diameter distribution histogram from the observed CAPs recorded by both extracellular and suction techniques.

Histological Procedures for Fixing the Nerve Bundel and Counting the Fiber Diameter Distribution: After the CAP recordings, we tied threads to each end of the frog sciatic nerve and first fixed in 10 % formal solution for 7 days. Following the fixation, the nerve bundle was fixed in a solution containing 50% xylol and 50% alcohol in incubator at 60 °C for 30-minutes. Thin sections were stained with hematoxylin-eosin, mounted on a microscope slide, and photographed (Zeiss Axioskop) with X40 magnification. Photomicrographs of a cross section of sciatic nerve bundles were scanned, and then the images were stored in a hard disk. The images were processed by NIH Image software (Rusband, W., National Institutes of Hèalth, USA, 1996) in Macintosh computer, and we mèasured the areas of the cross sections of each nerve fibers by digitising their circumferences including their myelin sheath.

RESULTS

The number of fibers of 5 nerves predicted from the photomicrographs of transverse section of the frog sciatic nerve bundles by using NIH Image software are given in Table-3.

The distribution, which have been predicted by the extracellular and suction CAP records by the application of inverse model and from the histological means, are given separately in Fig-3 for three nerves.

In order to see how the fiber diameter distribution histograms, which was obtained from CAP recorded by two techniques, correspond with the that obtained from histological means, three distribution histograms given in Fig-3 separately were graphed in the same axis for five nerves as shown in Fig-4.

To test the resemblance of fiber diameter distribution predicted from CAP recorded by extracellular and suction technics by the application of the inverse model with the measurements of histologic ones, we applied the chi-squared (χ^2) test by defining

$$\sum_{i=1}^{20} \frac{(\text{histological value - model value})^2}{\text{model value}}$$

The results of the test were given in Table-4.

DISCUSSION

Compound action potentials (CAPs) carry information about the underlying sources, i.e., the activity of the fibers of various diameters. To get valuable information about the nerve, recording technique and the model on which the calculation procedures depend

Table-3: The number of fibers predicted from histologic studies for five sciatic nerves.

Name of Experiment	Number of Fibers
Nerve-1	469
Nerve-2	594
Nerve-3	626
Nerve-4	364
Nerve-5	424

Table-4: Comparison of the distributions predicted by CAP analysis with that of obtained by histological study. * indicates p<0.05.

Name of Experiments	χ^2 values	
	extracellular	Suction
Nerve1	74.2*	17.0
Nerve2	31.3	71.3*
Nerve3	80.2*	121.2*
Nerve4	19.5	171.2*
Nerve5	20.9	162.0*

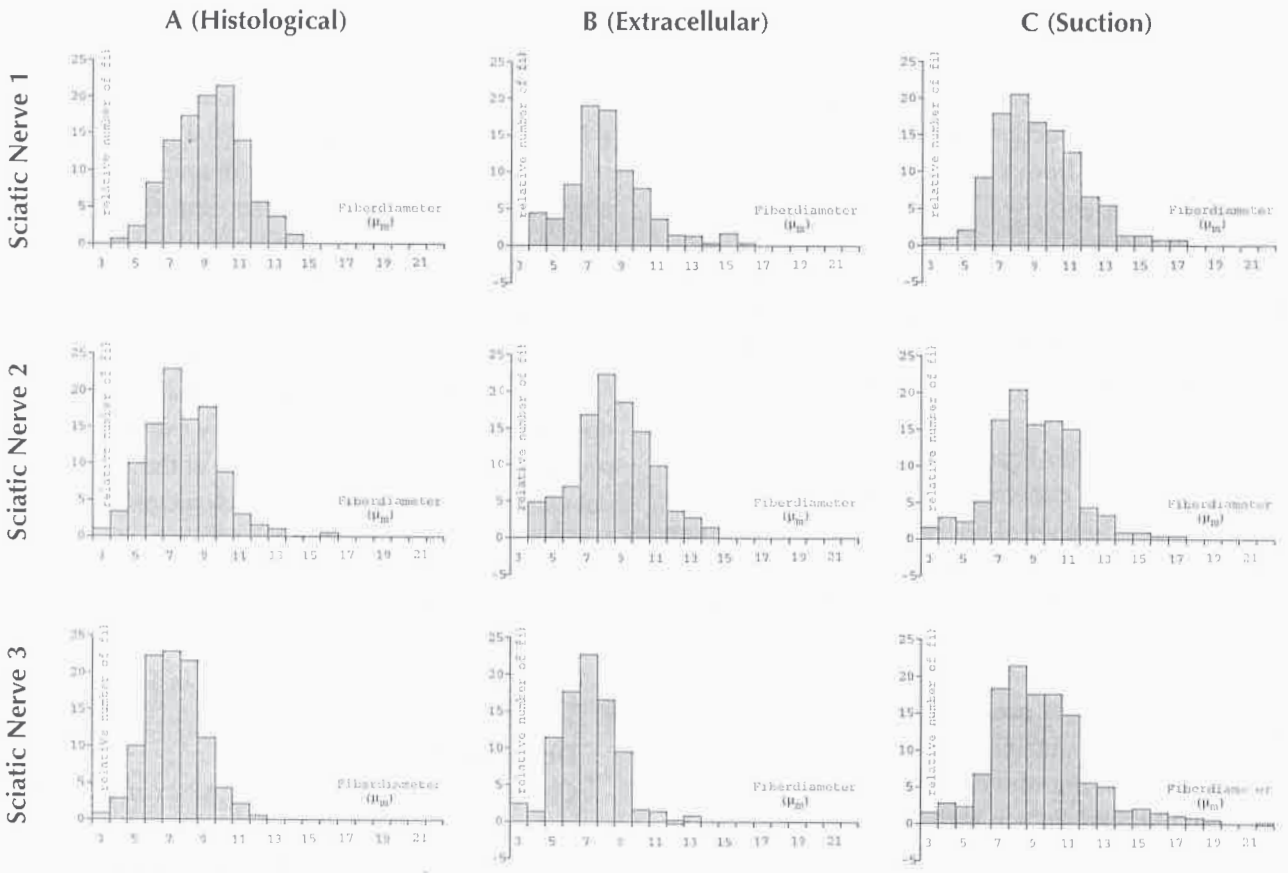

Figure 3: Fiber diameter distribution histograms of three different sciatic nerves (1-3) predicted from the extracellular (coulomb B) and suction (coulomb C) CAP records with the application of the model and from histological procedures (coulomb A).

on are very important. This study aimed to interrogate and compare two recording techniques in respects their applicability in determining the conduction velocity distribution in a nerve bundle. Attempts were started to estimate the distribution of fiber conduction velocities in a nerve bundle in 1927 by Gasser and Erlanger, then many investigator have been continuing since then (8,13,14,20). Each model requires a set of neurophysiological and bioelectrical approximations that allow a simplified description of propagation (9,10). This simplified description makes up the forward CAP model. Fitting the forward model to experimental CAP data solves the inverse problem.

Although, in this study, we mainly adopt the model proposed by Cummins et al. in our model we introduced the function

$$f(t)=A.\sin(t/\tau_{01}).\exp(-t/\tau_{02})$$

for SFAP waveshape which has two main advantages. First, it has smooth turnings as it is in actual case, instead of triangle proposed by the most researchers. Second, in addition to positive phase, it also has negative phase as it is in the frog sciatic nerve. SFAP duration may also be fitted to a given value by changing τ_{01} and τ_{02} for each fiber group.

For the conduction velocity-fiber diameter transformations for a fiber group, we adopt temperature dependence according to the equation (8) in methods.

Extracellular and suction CAPs are recorded at 2 cm distance of the stimulation site, and the data first processed in spreadsheet software. In this processing stage, 135 discrete values of a CAP starting from the pulse artifact have been taken, voltage conversion of data has been done and probable DC shifts in the signals have also been eliminated.

In the second processing stage, 137 discrete values of CAP signals were then transferred into another software capable matrix operations in accordance with the inverse model. The weighting coefficients

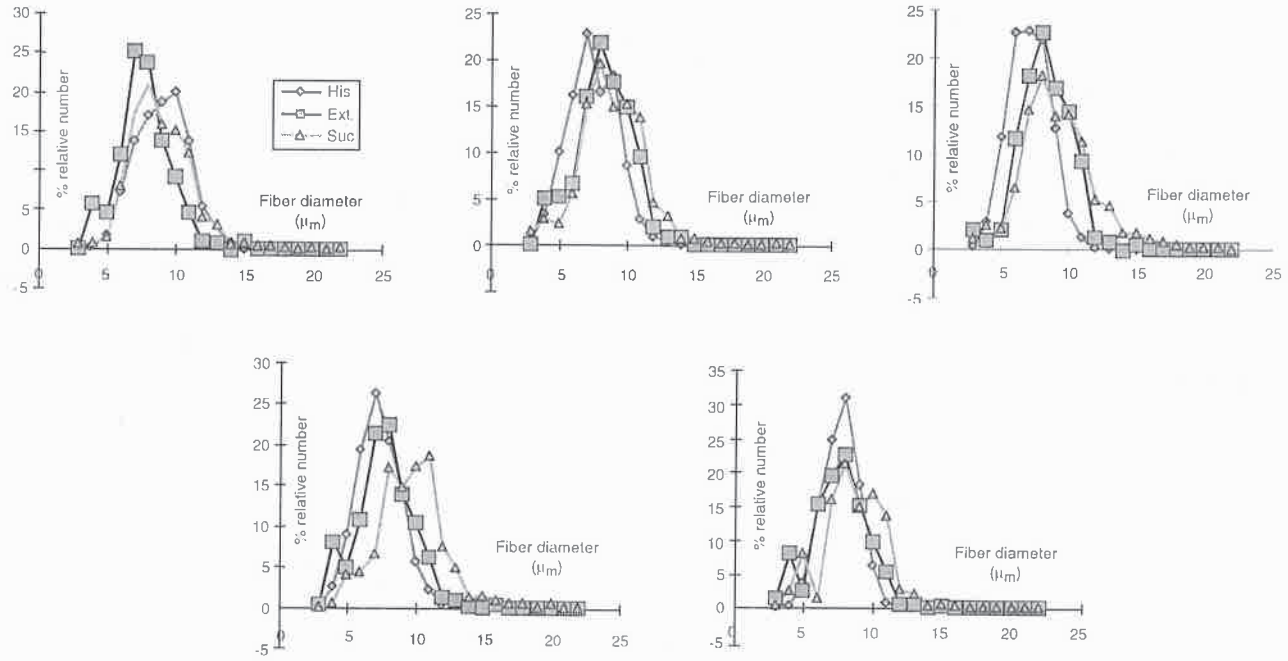

Figure 4: Relative number of fibers-fiber diameter curves predicted from extracellular and suction CAP and from histological procedures. The distributions were shown in the same axis in order to compare the histograms obtained from extracellular and suction recordings with that of histological one. The distributions for Nerve-1, Nerve-2, Nerve-3, Nerve-4 and Nerve-5 are given in a,b,c,d and e respectively.

(w) were determined. The weighting coefficients (w=H(m)A(d)) comprise two terms; one of them is relative number of fibers H(m) and the other term indicates the amplitude dependence A(d). This dependence has been postulated as $A(d)=d^p$. For further calculations, it is necessary to predict the value for p. In literature, many values have been proposed for p (8,9,12,13). Having proposed different values for p between 1 and 2, we have found iterativly p=1.6 as the most proper one. Then relative fiber diameter distributions were calculated from the weighting coefficients.

So as to consider which distribution, deduced from the CAP analysis, is best fitting with the actual distribution, it is necessary to construct another distribution from histology. So the same nerves were subjected to histological fixation procedures and sectional photomicrographs were taken. Photomicrographs were then processed in computer environment in order to measure the fiber diameters and to count the number of fiber properly.

In order to compare the coincidences, three distributions were graphed in the same coordinates as shown in Figure-4. We have applied Chi-squared test in order to compare FDDs predicted from CAPs recorded by extracellular and suction techniques with the histological distributions. It can be seen from Table-4 that, while 4 out of 5 FDDs predicted using suction recording differ significantly from the histological distributions, only 2 of 5 predictions differed significantly for the extracellular method.

From the results above, we conclude that the fiber diameter distribution histograms obtained by application of inverse model to the extracellularly recorded CAPs coincide with the histological distribution better than that of suction CAPs. Thus, in determination of fiber distribution of isolated nerve, the extracellular technique is more convenient than the suction technique.

In determining FDD, why suction findings coincide with histological distributions less than extracellular findings may be arisen from two reasons. First, in

suction technique, the resistance of the nerve segment which is outside the Ringer's solution at the stimulating electrode site and the resistance of the nerve segment which is inside the solution near the recording suction electrode site are different. Thus, unavoidable systematic errors may be arisen. The second, some uncertainty may arise in the distance between the suction electrode and stimulating electrode because of the pipette tip geometry. These two reasons may affect our results.

REFERENCES

1. Wells M.D., Gazoni S.N. A Method to Improve the Estimation of Conduction Velocity Distribution over a Short Segment of Nerve. IEEE Transaction on Biomedical Engineering. 1999, 46(9):1107-1120.
2. Rubinstein C.T., Shrager P. Remyelination of Nerve Fibers in the Transected Frog Sciatic Nerve. Brain Research. 1990, 524:303-312.
3. Caccia M.R., Osio M., Dezuanni E., Bevilacqua M., Bertora P.L., Salvaggio A., Mangoni A., Norbiato G. Nerve Conduction Velocity Distribution in Normal Subject and in Diabetic Patients without Clinical neuropathy I. Motor Nerve. Electromyogr. Clin. Neurophysiology. 1992, 32:403-409.
4. Caccia M.R., Osio M., Dezuanni E., Bevilacqua M., Bertora P.L., Salvaggio A., Mangoni A., Norbiato G. Nerve Conduction Velocity Distribution in Normal Subject and in Diabetic Patients without Clinical neuropathy II. Sensory Nerve. Electromyogr. Clin. Neurophysiology. 1992, 32:411-416.
5. Raymond S.A. Effects of Nerve Impulses on Threshold of Frog Sciatic Nerve Fibers. J. Physiol. 1979, 290:273-303.
6. Stegeman D.F., De Weerd J.P. Modelling Compound Action Potentials of Peripheral Nerves in situ. I. Model Description; Evidence for a Non-linear Relation Between Fibre Diameter and Velocity. Electroencephalography and clinc. Neurophysiology. 1982, 54:436-448.
7. Stys P.K., Ranson B.R., Waxman S. Compound Action Potential of Nerve Recorded by Suction Electrode: A Theoretical and Experimental Analysis. Brain Research. 1990, 546:18-32.
8. Cummins K.L., Perkel D.H., Dorfman L.J. Nerve Fiber Conduction-Velocity Distributions. I. Estimation Based on the Single-Fiber and Compound Action Potentials. Electroencephalography and clinc. Neurophysiology. 1979, 46:634-646.
9. Schoonhoven R., Stegeman D.F. Model and Analysis of Compound Nerve Action Potentials. Critical Reviews in Biomedical Engineering. 1991, 19(1):47-111.
10. Dorfman L.J. The Distribution of Conduction Velocities (DCV) in Peripheral Nerves. A Review. Muscle & Nerve. 1984, 7:2-11.
11. Gu D., Gander R.E., Chrichlow E.C. Determination of Nerve Conduction Velocity Distribution from Sampled Compound Action Potential Signals. IEEE Transactions on Biomedical Engineering. 1996, 45(8):829-838.
12. Waxman S.G. Cellular Aspects of Conduction in Myelinated Nerve Fibers in Relation to Clinical Deficit. In edd. Dorfman L., Cummins K.L., Leifer L. Conduction Velocity Distribution: A Population Approach to Electrophysiology of Nerve. Pp.1-15. Alan R. Liss. Inc.150 Fifth Avenue, New York. 1981.
13. Cummins K.L., Dorfman L.J., Perkel D.H. Nerve Fiber Conduction-Velocity Distribution. II. Estimation Based on Two Compound Action Potentials. Electroencephalography and Clinical Neurophysiology. 1979, 46:647-658.
14. Wijesinghe R.S., Gielen F.L.H., Wikswo J.P. A Model for Compound Action Potentials and Currents in a Nerve Bundle I: The Forward Calculation. Annals of Biomedical Engeneering. 1991, 19:43-72.
15. Hirose G., Tsuchitani Y., Huang J. A New method for Estimation of Nerve Conduction Velocity Distribution in the Frequency Domain 1986. Electro encephalography and Clinical Neurophysiologl. 63; 192-202.
16. Gasser H.S., Grundfest H. Axon Diameters in Relation to the Spike Dimentions and the Conduction Velocity in Mammalian A Fibers. J. Physiology. 1939, 127(3):393-414.
17. Kovacks Z., Jonson T., Sax D. Nerve Conduction Velocity Distributions: A Method Assuming Noisy Estimates of the Single Fiber Electrical Response. In edd. Dorfman L.J., Cummins K.L., Leifer L.J. Conduction Velocity Distribution: A Population Approach to Electrophysiology of Nerve. New York. Alan R. Liss inc. 1987, pp:85-111.
18. Sax D.S., Kovacs Z.L., Jhonson J.L., Feldman R. (1981). Clinical Applications of the Estimation of Nerve Conduction Velocity Distribution. In edd. Dorfman L.J., Cummins K.L., Leifer L.J. Conduction Velocity Distribution: A Population Approach to Electrophysiology of Nerve. New York. Alan R. Liss inc. pp:113-136.
19. Wijesinghe R.S., Gielen F.L.H., Wikswo J.P. (1991). A Model for Compound Action Potentials and Currents in a Nerve Bundle III: A Comparison of the Conduction Velocity Distribution Calculated from Compound Action Currents and Potentials. Annals of Biomedical Engeneering. 19:97-121.
20. Schoonhoven R., Stegeman D.F., Von Oosterom A., Dautzenberg G.F.M. (1988). The Inverse Problem in Electroneurography-I: Conceptual Basis and Mathematical Formulation. IEEE Transaction on Biomedical Engineering. 35(10):769-777.

MUCOID CYTOPLASMIC INCLUSIONS IN BLADDER CARCINOMA

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SUMMARY

Objective: *To determine the incidence of mucoid cytoplasmic inclusions (MCI) in transitional cell cancer of the bladder (TCC) and the relationship between MCI and histological grades.*

Materials and methods: *This study covered 70 patients with TCC diagnosed between 1996-1998 at the Pathology and Urology Department and 30 healthy individuals as a control group. Paraffin sections were stained with hematoxylin eosin and Periodic acid-schiff (PAS)/diastase. MCI were examined in each grade group.*

Results: *Mucoid cytoplasmic inclusions were observed at 35.71% in the TCC group and 10.0% in the control group (p< 0.05). The rate of inclusions was 18.75% in grade 1, 34.21% in grade 2 and 56.25% in grade 3 carcinomas (p< 0.05). The rate of MCI was correlated with the histological grade, with 'rarely' the most common form among all the types.*

Conclusions: *PAS positive cytoplasmic inclusions are seen more frequently in TCC than in normal bladder tissue, and the rate of MCI increases in high-grade tumors.*

Key words: *Mucoid cytoplasmic inclusions, bladder carcinoma, grade*

ÖZET

Mesane Karsinomunda Mukoid Sitoplazmik İnklüzyonlar

Amaç: *Mesanenin değişici epitel karsinomasında mukoid sitoplazmik inklüzyon insidansını belirlemeyi ve mukoid sitoplazmik inklüzyon ile histolojik derece arasında korelasyon olup olmadığını incelemeyi amaçladık.*

Materyal ve metod: *Çalışmaya SSK Ankara Hastanesi Patoloji ve Üroloji Bölümlerinde 1996-1998 yılları arasında değişici epitel karsinoması tanısı almış 70 olgu dahil edildi.30 sağlıklı kişide kontrol grubunu oluşturmaktaydı.Tüm olguların spesmenlerinin parafin kesitlerine hematoksilen eozin ve Periodic-acid-schiff (PAS)/diastaz boyası uygulandı. Işık mikroskobunda lamlar tüm histolojik derece grupları için mukoid sitoplazmik inklüzyonlar yönünden incelendi.*

Bulgular Değişici: *epitel karsinoması grubunda mukoid sitoplazmik inklüzyonlar %35.71 oranında ,kontrol grubunda %10.0 oranında izlendi (p<0.05). Histolojik derecesi 1 olan grupta (grade 1) inklüzyonların oranı %18.75, grade 2'de %34.21, grade 3 karsinomalarda %56.25 olarak izlendi.(p<0.05) Mukoid sitoplazmik inklüzyonların oranı histolojik derece ile korele bulundu.'Nadiren' diye tanımlanan sıklıkta izlenen formu en sık gözlenen formuydu.*

Sonuç: *PAS pozitif mukoid sitoplazmik inklüzyonlar mesanenin değişici epitel karsinomasında normal mesane dokusuna oranla daha sık olarak izlenmektedir.Ve tümörün histolojik derecesi arttıkça bu inklüzyonların görülme oranı artmaktadır.*

Anahtar kelimeler: *Mukoid sitoplazmik inklüzyonlar, mesane karsinomu, histolojik derece*

Neutral and mucoid substances become dense in the cytoplasm of normal or tumor cells, forming mucoid inclusions that are similar to globular structures (1). These globules are also called 'Melamed-Wolinska bodies' (2). Mucinous inclusions may be seen in different kinds of carcinomas, including transitional epithelial carcinoma and their metastasis (2). This interesting subject was described in 1992 by Donhuijsen et al. They also pointed out that there was little knowledge about the relationship between the incidence of mucoid cytoplasmic inclusions and their rates in different grades of TCC (3).

The objective of this study was to compare frequency of mucoid cytoplasmic inclusions in TCC and in normal bladder tissue and to determine their ratios in different TCC grades.

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MATERIALS AND METHODS

This retrospective study was performed on 70 patients admitted to our department from April 1996 to May 1998 with histopathologically proven transitional cell carcinoma of the bladder. Thirty patients who showed no bladder pathology during cystoscopies for inserting D-J catheter to ESWL were included as a control group. The TCC group comprised 62 male and eight female patients (median age 59.8 years, range 35-76). The control group comprised 28 male and two female patients (median age 56.9, range 32-74).

The TCC cases were classified according to the criteria of the World Health Organisation (WHO): Grade 1 (Group 1), Grade2 (Group 2), Grade 3 (Group 3). Paraffin sections were stained with hematoxylin-eosin. In addition, all slides were stained with PAS/diastase, which is more specific and sensitive for epitelial mucin than conventional methods (2). Extracellular PAS (+) mucoid material and intracytoplasmic apoptotic bodies were excluded when the presence of mucoid cytoplasmic inclusions were examined under light microscopy. Inclusion bodies were categorized according to the criteria of Renshaw et al (2):

- None: None seen in any microscopic area;
- Rarely: Less than 2 total in all areas;
- Few: Between total 2 in all areas to less than 1 in one high power magnification area;
- Often: 1-2 in one high power magnification area;
- Many: More than 2 in one high power magnification area;

Next, the distribution of mucoid cytoplasmic inclusions was evaluated according to grade. Of the 70 cases, 16 were Grade 1, 38 were Grade 2 and 16 were Grade3.

Chi-square method was used for the statistical analysis.

RESULTS

When the slides stained with PAS/diastase were examined, MCI were found in 29 (29.0%) cases. MCI were found in 8 (8.0%) cases in slides stained with hemotoxylin-eosin. There were no cases in which the hemotoxylin-eosin slide was positive and the PAS diastase slide negative.

MCI were observed in 25 of the 70 cases in the TCC group (35.71%) but only in 3 of the 30 (10.0%) cases in the control group ($p<0.05$). MCI were seen in 3 of the 16 (18.75%) cases in Group 1, in 13 of the 38 (34.21%) cases in Group 2 and in 9 of the 16 (56.25%) cases in Group 3 ($p<0.05$). The inclusions were seen rarely in all 3 cases in Group 1; rarely in 7 cases, few in 5 and often in 1 case in Group 2; rarely in 3 cases, often in 4 and many in 2 cases in Group 3 (Table 1).

In terms of size, the largest inclusion had the same diameter as the nucleus. The other inclusions were the same size as the lymphocytes or smaller than the lymphocytes. Most of the PAS/diastase (+) MCI were seen as dense globular structures with a halo around them (4) (Figure 1), although some of them had no border or halo. In 2 TCC cases, (one Grade 2 and one Grade 3 with prostatic invasion) the inclusions were seen as cytoplasmic lacunes with staining PAS (+) slightly peripherally PAS (+), which was similar to Donhuijsen's description. (3) (Figure 2).

DISCUSSION

Of all malignancies, transitional cell carcinoma of the urinary tract has the 4th highest incidence in men and 8th highest incidence in women (5). Millions of

Table 1. Relationship between cytoplasmic inclusions and histological grades.

	n	Rare	(%)	Few	(%)	Often	(%)	Many	(%)	TOTAL	(%)
Grade I	16	3	(18.75)	-	(0.00)	-	(0.00)	-	(0.00)	3	(18.75)
Grade II	38	7	(8.42)	5	(13.16)	1	(2.63)	-	(0.00)	13	(34.21)
Grade III	16	3	(18.75)	-	(0.00)	4	(25)	2	(12.5)	9	(56.25)
P*										<0.05	
TOTAL	70	13	(17.14)	5	(7.14)	5	(7.14)	2	(2.85)	25	(35.71)

* : Chi square test was used only between total grade levels.

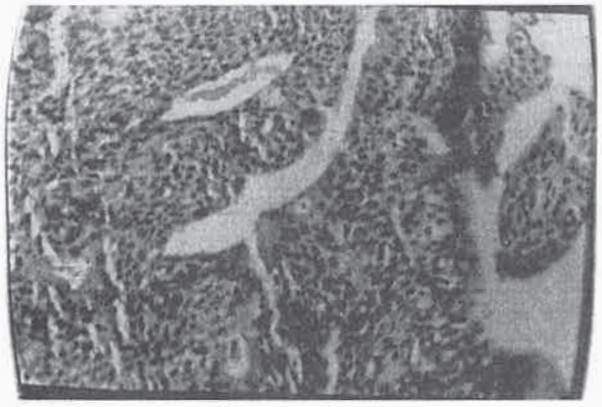

Figure 1. In high grade TCC, MCI are seen as globular structures with a halo around them. (PAS/diastase ¥ 100)

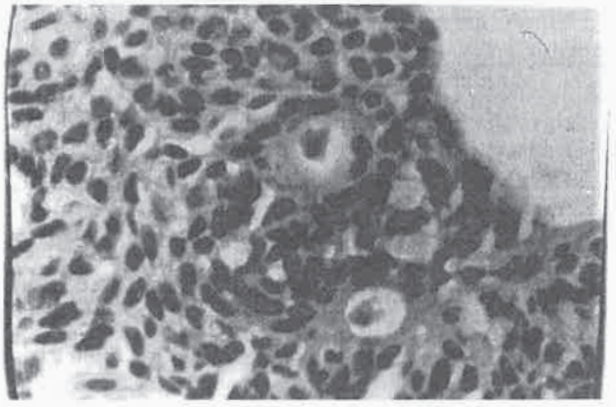

Figure 2. Cytoplasmic inclusions are similar to lacunes with slight PAS (+). (PAS/diastase ¥ 400)

people are affected by this tumor, with 200,000 male patients diagnosed with TCC each year. Thus, diagnosis, staging and prognosis of transitional epithelial carcinoma are of great importance. Specimens from these tumors must be examined carefully for primary focus, especially when metastatic tumors are diagnosed.

Mucin is composed of typical hexosamine molecules that contain carbohydrates greater then 50% and carbohydrate chains bound to nuclear proteins with covalent O-glycosidic ties (1). Mucin is also called mucopolysaccarides or glycosaminoglycans. Mucin is produced in the human body by glandular epithel and connective tissue. Normally, transitional epithelial cells include diffuse or globular mucoprotein deposits (6). Moreover, it is known that mucin production can be seen in chronic cystitis, adenocarcinoma of the bladder (7) and clear cell carcinoma (8) with or without the presence of glandular metaplasia. Outside of a few recent studies (9), it has not been widely shown that transitional epithelial carcinomas contain intracellular mucin. In 1992, Donhuijsen et al. reexamined cytoplasmic inclusions. They found that MCI were seen in 37% of transitional epithelial carcinoma cases and that the incidence increased with increasing grades (3). Samarantunga et al. reported that all transitional carcinomas produced mucin and had to be evaluated carefully for differential diagnosis from adenocarcinomas (10).

In this study, PAS/diastase (+) mucoid inclusions were observed at a rate of 35.71% in transitional epithelial carcinoma patients and 10% in the control group ($p<.0.05$) The incidence of mucin increased with the increasing grades. They were found at a rate of 18.75% in Grade 1 tumors, 34.21% in Grade 2 tumors and 56.25% in Grade 3 tumors ($p<0.05$). The number of cytoplasmic mucoid inclusions increased in high grade tumors. The 'rarely' form was the one most observed among all the forms described above according to Renshaw's criteria, especially in Grade 1 tumors. (Table 1).

Cytoplasmic mucoid inclusions are seen in different types of carcinomas such as adenocarcinoma of the gastrointestinal tract, lung adenocarcinoma, pulmonary blastoma, primary intracranial yolk sac tumors, breast carcinoma, hepatocellular carcinoma, hepatic sarcoma and Caposi sarcoma (11). For this reason, in metastasis with unknown primary foci, when PAS(+) cytoplasmic inclusions are observed, transitional epithelial carcinoma as well as other possible carcinomas may be considered. (2). Immunohistochemical examinations such as CEA, Leu-M1, cytokeratin 8-18, HCG, SP-1 and Cathepsin D help to distinguish the metastasis of TCC from other tumors. Observing pleomorphic microvilluses in electron microscopy may also be useful in differential diagnosis (12).

Cytoplasmic mucoid inclusions may be important factors in the diagnosis and prognosis of TCC. With this study, we aimed to reemphasize the importance of this subject. However, additional studies with lon-

ger follow-ups are necessary.

REFERENCES

1. Allsbrook WC, Simms WW. Histochemistry of the prostate. Human Pathol 1992; 23:297-305
2. Renshaw AA. Intracytoplasmic eosinophilic inclusions (Melamed-Wolinska bodies). Association with metastatic transitional cell carcinoma in pleural fluid. Acta Cytol 1997; 41(4):995-8
3. Donhuijsen K. Mucoid cytoplasmic inclusions in urethelial carcinomas. Hum Pathol 1992; 23(8):860-4
4. Yang GC. Morphogenesis of inclusion bodies of urethelial carcinoma: a case study. Mod Pathol 1996; May, 9(5):566-70
5. Pleshner NE, Herr HW, Stewart AK, Murphy GP, Mettline C, Merck HR. The national cancer data report on bladder carcinoma. Cancer 1996; 77:1505-13
6. Monis B. Some histochemical observations on transitional epithelium on man. J Histochem 1967; 15(8):475-81
7. Alroy J. Primary adenocarcinomas of human urinary bladder. Wirchows Arch 1981; 393:165-81
8. Choi H. Primary signet ring cell carcinoma of the urinary bladder. Cancer 1984; 53:1985-90
9. Tucker E. A new inclusions of the visceral epithelium of the renal pelvis. The presence of these inclusions in a papillary carcinoma of the kidney and its metastases . Cancer 1959; 12:1052-57
10. Samaratunga H. Letter to Donhuijsen et al. Hum Pathol 1993; 24(8):929-30
11. Scroggs MW. Eosinophilic intracytoplasmic globules in pulmonary adenocarcinomas. Hum Pathol 1989; 20(9):845-49

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QT INTERVAL DISPERSION: A NON-INVASIVE MARKER OF ISCHEMIC INJURY IN PATIENTS WITH UNSTABLE ANGINA PECTORIS?

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SUMMARY

Prognostic assessment of unstable angina pectoris is a common clinical problem for physicians. Markers of myocardial cell injury, serial electrocardiographic findings and ST segment monitoring had been largely studied for prognosis. We investigated the relation between myocardial injury with the value of troponin T and QT interval dispersion in hospitalized unstable angina patients. This was a prospective study that included adult patients who had been admitted to the emergency department with Braunwald class IIIB unstable angina pectoris. Sixty-five patients were enrolled in the study (mean age of 56±9 years, 40 male and 25 female). Cardiac troponin T was assayed, and QT dispersion was calculated by surface ECG. Forty-six patients with troponin T <0.1 ng/ml and 19 patients with troponin T levels ≥0.1 formed Group 1 and Group 2, consecutively. The significance of changes were measured using Student's unpaired t tests and chi-square tests. There were no significant differences in the clinical characteristics or ECG findings between the two groups. The mean QT dispersion was significantly greater in patients with elevated troponin T level. QT interval dispersion was found to be a non-invasive marker of ischemic cellular injury in patients with Braunwald class IIIB unstable angina, and we recommend it is used for identification of high-risk patients.

Key words: *QT dispersion, troponin T, unstable angina pectoris*

ÖZET

QT İnterval Dispersiyonu Kararsız Angina Pektorisli Hastalarda İskemik Hasarın Non-İnvazif Bir Belirleyicisi Olabilir mi?

Kararsız angina pektorisli hastaların prognostik yönden değerlendirilmesi klinisyenler için sorun oluşturmaktadır. İskemik hasar belirleyicileri olarak seri elektrokardiyografik bulgular ve ST segment monitorizasyonu prognostik yönden yaygın olarak çalışılmıştır. Bu çalışmada kararsız angina pektoris nedeniyle hospitalize edilen hastalarda troponin T seviyeleri ve QT intervali dispersiyonu arasındaki ilişki incelenmiştir. Prospektif olarak kararsız angina pektoris (Braunwald grup 3B) tanısı ile hospitalize edilen hastalar çalışmaya alındı. 65 hasta incelendi (yaş ortalaması 56 ± 9, 40'ı erkek 25'i kadındı). Kardiak troponin T ölçümleri ve yüzey EKG'sinden QT dispersiyonu değerleri hesaplandı. Troponin T değeri 0.1 ng/ml'den düşük olan 46 hasta birinci grubu, troponin T değeri 0.1 ng/ml veya daha fazla olan 19 hasta ise ikinci grubu oluşturdu. İstatistiki yöntem olarak "unpaired student t testi ve ki-kare testi" kullanıldı. Grup bir ve iki arasında klinik karakteristikler ve EKG yönünden fark yoktu. Ortalama QT dispersiyon değerleri troponin t değerleri yüksek olan grup ikide istatistiki olarak anlamlı ölçüde yüksekti.Sonuç olarak QT interval dispersiyonunun Braunwald grup 3B kararsız angina pektorisli hastalarda iskemik hücresel hasarın non-invazif olarak gösterilmesinde yardımcı olacağı ve yüksek riskli hastaların tanınmasına olanak sağlayacağı kanaatine vardık.

Anahtar kelimeler: *Kararsız angina pektoris, QT dispersiyonu, troponin T.*

Identification of patients with acute chest pain at high risk of cardiovascular complications is a common clinical problem for physicians. The surface electrocardiogram (ECG) has been one of the most studied parameters used for this purpose (1,2,3,4). The QT interval on the surface ECG is a measure of the total time of ventricular depolarization and repolarization. Regional differences in ventricular repolarization are reflected as differences in QT intervals in leads that correspond to different parts of the myocardium. This heterogeneity is called QT interval dispersion. Increased QT interval dispersion decreases the threshold for ventricular tachycardia and is associated with the risk of increased mortality (5,6,7,8,9). Creatine kinase (CK) and its isoenzyme CK-MB have been used for diagnosis of myocardial injury for more than a decade. Sing-

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le values of these tests have limited sensitivity and specificity for detection of myocardial infarction, and some data suggest that elevation in cardiac troponin T (cTnT) may be useful for detection of less severe degrees of myocardial injury that may occur in some patients with unstable angina (10,11).

Prior research has demonstrated that troponin T has excellent sensitivity for diagnosis of acute myocardial infarction and may also be useful for prognostic stratification of patients with unstable angina pectoris (12,13,14,15). In this prospective study, we investigated the relation between myocardial injury and the value of troponin T and QT interval dispersion in hospitalized unstable angina patients.

MATERIALS AND METHODS

Patient population: This was a prospective study including adult patients who had been admitted to the emergency department with Braunwald class IIIB unstable angina pectoris from September 1998 through April 1999, with a chief symptom of anterior or precardial chest pain that could not be explained by any other obvious reason. Acute myocardial infarction patients with ST segment elevation, patients with more than 3 mm horizontal or downsloping ST segment depression accompanied by long lasting (>30 minutes) severe chest pain and patients with diagnostic increase (≥2 of normal value) in serum levels of CK-MB in the 24 hours after admission were diagnosed as acute non-Q myocardial infarction by the responsible physician and not included in the study population. Patients with intraventricular conduction delay (QRS duration ≥120 msec), atrial fibrillation and prior myocardial infarction were also excluded from the study. Sixty-five patients with Braunwald class IIIB unstable angina pectoris were included in the final study population.

Data Collection: Clinical data were collected from emergency department evaluations including the patients' age, sex, history, physical examination and ECG. Blood was obtained at the time of presentation for cardiac enzyme assay and repeated every eight hours in the charge of the responsible physician.

Cardiac troponin T was assayed using excess serum from routine phlebotomy in the emergency department in the first 24 hours. All patients had measurements of troponin T taken one or more times after the first eight hours of their arrival in the emergency department. Troponin T was measured by an immunoassay procedure that uses complementary monoclonal antibodies. Analysis was performed on the ES-300 (Boehringer Mannheim Corporation): the upper limit of the reference interval was 0.1 ng/ml.

QT analysis: Standard electrocardiogram with simultaneous 12-lead acquisition was recorded at 50 mm/s. A blinded observer measured the QT intervals manually with calipers from the onset of the QRS to the end of the T wave defined as the return to the TP baseline. When U waves were present the QT interval was measured to the nadir of the curve between the T and U waves. Three consecutive cycles were measured in each of the standard 12 leads, and a mean QT was calculated from the three values. When the end of the T wave could not be identified the lead was not included. QT was corrected for heart rate according to Bazett's formula: $QTc = QT / RR^{1/2}$. A minimum of six leads were required to calculate QT dispersion. The QT dispersion was defined as the difference between the maximum and minimum QT interval occurring in any of the 12 electrocardiographic leads.

STATISTICS

The results were analyzed with the statistical package for social sciences. Continuous variables are presented as a mean ± SD. The significance of changes were calculated using Student's unpaired t tests and chi-square tests. A value of $p<0.05$ was regarded as significant.

RESULTS

Sixty-five patients were enrolled in the study (mean age of 56±9 years, 40 (61.5%) male and 25 (38.5%) female. Four (6%) patients had previous CABG operations and seven (11%) patients had undergone previous percutaneous coronary angioplasties (Table 1). We divided the patients into two groups according to troponin T levels. Forty-six patients with troponin T <0.1 ng/ml formed Group 1 and 19 patients with troponin T levels ≥0.1 formed Group 2. There were no significant differences in clinical characteristics or ECG findings between the two groups. All patients received aspirin (300mg/day) and were treated with nitrates (n=60), calcium antagonist (n=26), beta blockers (n=47) and heparin (n=58).

Table 1: Characteristics of study population

Age	56±9 (37-78)
Sex (male)	40 (61.5%)
Mean heart rate (beat/min)	71±8 (58-104)
Previous CABG (n)	4 (6.6%)
Previous PTCA (n)	7 (10.8%)
ECG at presentation (n)	
ST depression	36 (55%)
T inversion	29 (45%)
cTnT (n)	
<0.1 ng/ml	46 (70.7%)
≥% 0.1 ng/ml	19 (29.3%)

Table 2 shows the results of the QT analysis at 24 hours. Even though calculated QTc intervals were similar between the two groups, the mean QT dispersion was significantly greater in patients with elevated troponin T levels (p=0.02).

DISCUSSION

Prognostic assessment of unstable angina pectoris resulting from subtotal thrombotic occlusion of the coronary arteries is a common clinical problem for physicians. In clinical practice, prognosis is based on clinical history, objective findings and laboratory data. Early identification of patients with high-risk angina, however, has largely focused on the markers of myocardial cell injury, serial electrocardiographic findings and ST segment monitoring (13,14,15,16, 17,18).

Table 2: Clinical and QT analysis of patient groups

	cTn T (+) n=19	**CTn T (-) n=46**	**p**
Age	57±10	60±9	NS
Sex (male:n)	10 (53%)	30 (65%)	NS
ST depression(n)	10 (53%)	26 (57%)	NS
T inversion (n)	9 (47%)	20 (43%)	NS
Heart rate (beat/min)	76±8	72±12	NS
QTc(msec)	414±26	426±22	NS
QT dispersion (msec)	75±12	39±17	0.02

Troponin T is one of the most studied laboratory parameters, and potentially available serum levels of cardiac troponin T have significantly greater prognostic value than other laboratory parameters in patients with unstable angina pectoris (13,14,19). Multivariate analysis has shown that serum level of troponin T is an independent factor with high sensitivity and specificity for poor prognosis (14).

QT interval dispersion reflects regional variations in ventricular repolarization and cardiac electrical instability, which is a substrate for ventricular arrhythmia. Previous studies have shown that QT interval dispersion increases during episodes of myocardial ischemia in patients with coronary artery disease, but only a limited number of studies so far have examined the relation between the extent of myocardial ischemia and the degree of QT interval dispersion (20,21,22,23,24).

Our study is the first to examine the degree of QT dispersion with troponin T levels in high-risk patients with Braunwald class IIIB unstable angina. Elevations of cardiac troponin T were detected in the first 24 hours among 19 (29.2 %) patients of the 65 patients with unstable angina. We determined a significant association of dispersion of ventricular repolarization (the difference between maximum and minimum QT interval measurements in any of the 12 leads on a standard electrocardiogram) with cellular injury in patients with class IIIB unstable angina who had elevated troponin T levels (75±12 msec vs 39±17 msec, p=0.02). This association was independent of age, sex and drug assignment.

This study also shows that microscopic-level injury detected by elevated troponin T may result in modification of ventricular repolarization in large areas of the myocardium which can be detected by surface ECG. That level of injury may change extracellular potassium and/or intracellular hydrogen, which modify ventricular repolarization hours after the ischemic episodes and also explains considerable change in QT behavior between the leads. In conclusion, increased QT interval dispersion is a non-invasive marker of ischemic cellular injury in patients with Braunwald class IIIB unstable angina. Since QT interval dispersim is well associated with elevated cardiac troponin T levels, we recommend it is used for identification of high-risk patients.

REFERENCES

1. Schwartz PJ, Wolf S. QT interval prolongation as predictor of sudden death in patients with myocardial infarction. Circulation 1978; 57:1074-1077.
2. Ahnve S, Helmers C, Lundman T, Rehnavist N, Sjogren A. Qtc intervals in acute myocardial infarction: first year prognostic implication. Clin Cardiol 1980; 3:303-308.
3. Whelan K, Mukharji J, Rude RE, et al. Sudden death and its relation to QT interval prolongation after acute myocardial infarction: two-year follow-up. Am J Cardiol 1986;57:745-750.
4. Puddu PE, Bourassa MG. Prediction of sudden death from QTc interval prolongation in patients with chronic ischemic heart disease. J Electrocardiol 1986; 19:203-212.
5. Zarebo W, Moss AJ, Cessie S. Dispersion of ventricular repolarization and arrhythmic cardiac death in coronary artery disease. Am J Cardiol 1994; 74:550-5536.
6. Pye M, Quinn AC, Cobbe SM. QT interval dispersion: a non-invasive marker of susceptibility to arrhythmia in patients with sustained ventricular arrhythmia. Br Heart J 1994; 71:511-514.
7. Higham PD, Furniss SS, Campbell RW. QT dispersion components of the QT interval in schemia and infarction. Br Heart J 1995; 73:32-36.
8. Potratz J, Djonlagic H, Mentzel H. Prognostic significance of QT dispersion in patients with acute myocardial infarction. (Abstract) Eur Heart J 1993; 14:254.
9. Perkiomaki JS, Koistinen MJ, Yli Mayry S, Huikuri HV. Dispersion of QT interval in patients and without susceptibility to ventricular tacharrhythmias after previous myocardial infarction. J Am Coll Cardiol 1995; 26:174-179.
10. Gerhard V, Katus HA, Rakvilde J, Hamm CW. Troponin T in suspected ischemic myocardial injury compared with mass and catalytic concentration of S-creatine kinase isoenzyme MB. Clin Chem 1991; 37:1405-1411.
11. Ohman EM, Armstron PW, Christenson RG, Granger CB, Katus HA, Hamm Cw, et al. Cardiac troponin T levels for risk stratification in acute myocardial ischemia. J Am Coll Cardiol 1995; 25:574-581.
12. Hamm CW, Ravkilde J, Gerhardt W. The prognostic value of serum troponin T in unstable angina. N Engl J Med 1992; 327:146-150.
13. Lindahl B, Venge P, Wallentin L. Relation between troponin I and the risk of subsequent cardiac events in unstable coronary artery disease. Circulation 1996; 93:1651-1657.
14. Rebuzzi AG, Quaranta G, Liuzzo G, Caligiuri G, Lanza GA, Gallimore R, Grillo RL, Cianflone D, Biassuci LM, Maseri A. Incremental prognostic value of serum levels of troponin T and CRP protein on admission in patients with unstable angina pectoris. Am J Cardiol 1998; 82:715-719.
15. Wu AHB, Abbas SA, Green S, Pearsall L, Dhakam S, Azar R, Onoroski M, Senaie A, McKay R, Waters D. Prognostic value of cardiac TT in unstable angina pectoris Am J Cardiol 1995; 7610:970-972.
16. Betriu A, Heras M, Cohen M, Fuster V. Unstable angina: outcome according to the clinical presentation. J Am Coll Cardiol 1992; 19:1659-1663.
17. Larger A, Freeman MR, Armstrong PW. ST segment shift in unstable angina: pathophysiology and association with coronary anatomy and hospital outcome. J Am Coll Cardiol 1989; 3:1495-1502.
18. Nyman I, Areskog M, Areskog NH, Swahn E, Wallentin L, and RISK study group. Very early stratification by electrocardiogram at rest in man with suspected unstable coronary heart disease. J Intern Med 1993; 234:293-301.
19. Mulcahy R, Daly L, Graham I, Hickey N, O'Donogue S, Qwens A, Ruana P, Tobin G. Unstable angina: natural history and determinant of prognosis. Am J Cardiol 1981; 48:525-528.
20. Cin VG, Celik M, Ulucan S. QT dispersion ratio in patients with unstable angina pectoris (a new risk factor?). Clin Cardiol 1997; 20(6):533-535.
21. Zareba W, Moss AJ, Cessie S. Dispersion of ventricular repolarization and arrhythmic cardiac death in coronary artery disease. Am J cardiol 1994; 74:550-553.
22. Higham PD, Campbell RWF. QT dispersion. Br Heart J 1994; 71:508-510.
23. Lee HS, Cross SJ, Rawles J. QTc dispersion in patients with coronary artery disease. Effect of exercise, dobutamine and dipyridamole on myocardial stress (abstract) Eur Heart J 1993; 14:210.
24. Stierle U, Giannitsis E, Sheikhzadeh A, Krüger D, Schmücker G, Mitusch R, Potratz J. Relation between QT dispersion and the extent of myocardial ischemia in patients with three-vessel coronary artery disease. Am J Cardiol 1998; 81:564-568.

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THE EFFECTIVENESS OF OMEPRAZOLE AND LANSOPRAZOLE ON SYMPTOMATOLOGY AND ULCER HEALING, AND ON CLEARENCE OF HELICOBACTER PYLORI IN PATIENTS WITH DUODENAL ULCER

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SUMMARY

This study compares the effectiveness of Omeprazole and Lansoprazole on ulcer healing, symptomatology and eradication of Helicobacter pylori (HP) in patients with duodenal ulcers. In a double-blind, parallel group trial, 24 patients (Group I) received Omeprazole (20 mg) each morning before breakfast and an additional 24 patients (Group II) received Lansoprazole (30 mg). Endoscopic examinations and CLO tests were performed on all patients, and blood samples were taken for liver transaminases, urea, creatinine, FSH, LH, testosterone, estradiol and progesterone.

Duodenal ulcers reached scar stages earlier and higher clearance rates for HP were attained in more patients receiving Lansoprazole (17 out of 24) than Omeprazole (15 out of 24). There was no statistical difference for the relief of symptoms in the two groups after one and two months of therapy, nor was there any statistical difference for FSH, LH, testosterone, estradiol or progesterone levels of the two groups before or after treatment.

In conclusion, Lansoprazole achieved quicker healing rates on ulcers and higher clearance rates for HP than Omeprazole after one and two months of treatment.

Key words: *Duodenal ulcer, Helicobacter pylori, Omeprazole, Lansoprazole.*

ÖZET

Omeprazol ve Lansoprazole'ün Ülsere Etkileri

Bu çalışmada omeprazol ve lanzoprazolün dodenal ülserli hastalarda ülser iyileşmesi, semptomatoloji ve Helicobacter pylori(HP) üzerine olan etkileri araştırılmıştır. Çalışma çift-kör yapılmıştır. Omeprazol 24 hastaya kahvaltıdan önce 20 mg (Grup 1), lansoprazol ise 30 mg (Grup 2) verildi. Her vakada endoskopik muayene ve CLO test yapıldı. Serum transaminazları, üre, kreatinin, FSH, LH, testosteron, östradiol ve progesteron düzeyleri için kan alındı.

Lansoprazol kullanan 24 hastanın 17'sinde, omeprazol kullanan 24 hastanın ise 15'inde ülser skar safhasında saptandı. HP klerensi de lansoprazol kullananlarda daha yüksekti. Tedaviden 1 ve 2 ay sonra semptomatik düzelme yönünden anlamlı fark bulunamadı. Tedavi öncesi ve tedavi sonrası gruplar arasında serum FSH, LH, testosteron, östradiol ve progesteron düzeyi yönünden fark bulunmadı.

Sonuç olarak; tedaviden 1 ve 2 ay sonra lansoprazol kullananlarda ülser iyileşmesi ve HP klerensi daha yüksek bulundu.

Anahtar kelimeler: *Duodenal ülser, Helicobacter pylori, Lansoprazol, Omeprazol.*

The treatment of duodenal ulcers is based on the inhibition of gastric acid secretion and on the eradication of Helicobacter pylori (HP). Histamine H_2 receptor antagonists and proton-pump inhibitors such as Omeprazole and Lansoprazole have successfully inhibited basal and stimulated acid secretion (1). Lansoprazole is a newly substituted benzimidazole that selectively inhibits the proton pump both in vitro and in vivo (2).

The role of the treatment of HP in healing duodenal ulcers has recently come to be well understood (3). Eradication of HP in patients with duodenal ulcers provides faster healing, less recurrence, and fewer complications of duodenal ulcers. Omeprazole and Lansoprazole achieve faster ulcer healing, faster symptom relief and reduction in the density of HP than histamine H_2 receptor antagonists (4-6). However, there have not been sufficient studies comparing the effecti-

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veness of Omeprazole and Lansoprazole on ulcer healing, symptomatology and the eradication of HP in patients with duodenal ulcers.

The present study compares the effectiveness and safety of Omeprazole and Lansoprazole in the treatment of duodenal ulcers and in the eradication of HP.

MATERIALS AND METHODS

The study was designed as a double-blind parallel group trial. Patients with endoscopically proven active-stage ulcers of at least five mm in diameter were included in the study. Twenty-four patients (15 male, 9 female) with duodenal ulcers were treated with 20 mg of Omeprazole, administered each morning before breakfast, for two months (Group I). The mean age of this group was 37.4 (19-59) years. Twenty-four patients (18 male, 6 female) with duodenal ulcers were treated with 30 mg of Lansoprazole, administered each morning before breakfast, for two months (Group II). The mean age of this group was 35.16 (18-59) years.

Each patient was questioned and notes taken regarding retrosternal pain, nausea and/or vomiting, night burns, gas, smoking, alcohol and drug use before endoscopy. Endoscopic examinations were performed before the treatment and one month (first control) and two months (second control) after the treatment.

Ulcers were classified as Active Stage 1, Active Stage 2, Healing Stage 1, Healing Stage 2, Scar Stage 1 or Scar Stage 2, according to ulcer base, regenerative epithelium, erythema and edema, and the convergence of mucosal fold (7). CLO tests were taken at each endoscopic session. Blood samples were performed before treatment and after each control to evaluate serum levels of FSH, LH, testosterone, estradiol, progesterone, liver transaminase, urea and creatinine.

Qui-Square tests and Student-t tests were used for statistical analysis.

Criteria for exclusion from this study were; age (below 18 or above 80 years); grosses and lactations; complicated ulcers such as gastrointestinal bleeding, pyloric stenosis, perforations; secondary organic diseases; any prior operation to decrease stomach acid; heavy alcohol consumption; use of anti-ulcer drugs and/or NSAID medication.

RESULTS

Symptoms of patients are summarized in Table 1. All symptoms had disappeared in both groups as of the first control. There was no statistical difference concerning selection of the patients in the two groups or in symptoms of patients before treatment or one month after treatment.

Table 1. Diary of patients treated with Omeprazole and Lansoprazole before treatment

	Omeprazole (Group I)		Lansoprazole (Group II)	
	N	%	N	%
Retrosternal pain	18/24	75	24 /24	100
Nausea and/or vomiting	14/24	58.3	11/24	45.8
Night pains	18/24	95	14/24	58.3
Gas	15/24	62.5	17/24	70.8
Smoking	10/24	41.6	9/24	37.5
Alcohol	1/24	4.1	1/24	4.1
Smoking & Alcohol	4/24	16.6	1/24	4.1

In Group I, 16 patients were in Active Stage 1 and eight patients in Active Stage 2. CLO tests were positive in 23 patients. At the first control, six patients were in Healing Stage 1, three patients in Healing Stage 2, 11patients in Scar Stage 1 and four patients in Scar Stage 2. CLO tests were negative in eight patients. At the second control, two patients were in Healing Stage 1, four patients in Healing Stage 2, nine patients in Scar Stage 1 and nine patients in Scar Stage 2. CLO tests were negative in 14 patients (Table 2).

In Group II, 16 patients were in Active Stage 1 and eight patients were in Active Stage 2 before treatment. CLO tests were positive in 23 patients. At the first control, five patients were in Healing Stage 1, two patients were in Healing Stage 2, 11 patients were in Scar Stage 1, and six patients were in Scar Stage 2. CLO tests were negative in 13 patients. At the second control, two patients were in Healing Stage 1, one pa-

Table 2. Results of Omeprazole therapy in duodenal ulcer patients

			1st Control	*2nd Control*
Omeprazole	A1:16/24	66.6 %	H1:6/24	H1:2/24
	A2:8/24	33.3 %	H2:3/24	H2:4/24
			S1:11/24	S1:9/24
			S2:4/24	S2:9/24
CLO Test	23/24 (+)		9/24 (-)	15/24 (-)

tient in Healing Stage 2, eight patients in Scar Stage 1 and 13 patients in Scar Stage 2. CLO tests were negative in 20 patients (Table 3).

At the first control, 15 patients in Group One and 17 patients in Group Two were in Scar Stage. At the second control, 18 patients in Group I and 21 patients in Group II were in Scar Stage.

Even though there was no significant statistical difference between the two groups, Lansoprazole caused more patients to progress to scar stage. CLO tests were negative in 14 patients in Group I and in 20 patients in group II. There was no significant statistical difference between the two groups, but Lansoprazole also caused more patients to have negative CLO tests.

We did not find any differences for FSH, LH, testosterone or estradiol levels between the two groups before and after treatment. Both drugs were found safe to use, and no side effects were encountered.

DISCUSSION

Duodenal ulcers can be successfully treated with proton pump inhibitors because they inhibit basal and stimulated gastric acid output (8). In addition to this property, they may suppress the growth of HP (9). Eradication of HP in patients with duodenal ulcers will decrease the recurrence rate of the disease. A number of studies emphasize that Omeprazole and Lansoprazole are potent and specific inhibitors of HP urease (10), and that the inhibitory effect of Lansoprazole is four times greater than Omeprazole.

Omeprazole and Lansoprazole have in vitro antibacterial effects on HP (5). These effects increase when used in combination with an antibiotic such as amoxicilline (11). Nagata et al showed that the inhibitory action of amoxicilline on the growth of HP was independent of the inhibitory action on urease(10). Lansoprazole increases tissue basic fibroblast growth factor by inhibiting the breakdown of basic fibroblast growth factor by acid and pepsin and promotes gastric ulcer healing in humans (12). Lansoprazole binds directly to neutrophil lysosomes and inhibits oxygen-derived free radical production from neutrophils activated by HP and reduces neutrophil-dependent gastric mucosal injury associated with HP (13).

In our study, we found that Lansoprazole had higher clearance rates of HP than Omeprazole (Table 2 and Table 3).

Fasting gastrin levels and antral G-cell density increase during treatment with Lansoprazole and decrease to normal one month after cessation of Lansoprazole treatment. Enterocromaphin cells and D cells containing somatostatin do not change during treatment (14). When Ranitidine and Lansoprazole were compared for healing and relief of symptoms in duodenal ulcer patients, Lansoprazole was superior to Ranitidine (4,6).

Petit et al compared Omeprazole and Lansoprazole treatment in duodenal ulcer patients and found that the duration needed for the relief of ulcer pain was two days with Lansoprazole and three days with Omeprazole; healing rate in two weeks was 74% with Lansoprazole, and 68% with Omeprazole. There was no difference in healing rates for the two drugs after four weeks of treatment (15). Ekström et al compared Omeprazole and Lansoprazole in duodenal ulcer patients. Healing rates of ulcers after two and four weeks of treatment with Omeprazole and Lansoprazole were 82.3% and 87.2% and 96.7% and 97.7%, respectively. There was no difference in the relief of symptoms between the two groups (16). These results are compatible with our results.

In another study, the ulcer-healing rate was found to be 82.1% in two weeks and 96.2% in four weeks with Omeprazole and 86.2% in two weeks and 97.1% in four weeks with Lansoprazole (17).

Most anti-ulcer drugs are capable of healing peptic ulcers in four weeks. Among these, physicians may prefer the one that provides the most rapid disappearance of ulcer complaints and healing of the ulcer and which possesses the least side effects.

In conclusion, although there were no statistical differences between the two treatment groups in terms of symptom relief or ulcer healing, Lansoprazole was found to achieve slightly higher numerical rates of duodenal ulcer healing and higher rates of HP clearance than Omeprazole.

Table 3. Results of Lansoprazole therapy in duodenal ulcer patients

			1st Control	*2nd Control*
Lansoprazole	A1:16/24	66.6 %	H1:5/24	H1:2/24
	A2:8/24	33.3 %	H2:2/24	H2:1/24
			S1:11/24	S1:8/24
			S2:6/24	S2:13/24
CLO Test	23/24 (+)		14/24 (-)	20/24 (-)

This study also found that there were no statistical differences in FSH, LH, estradiol, progesterone or testosterone levels before and after Omeprazole and Lanpsoprazole treatment.

Consequently, although both Omeprazole and Lansoprazole are devoid of any major side effects and both have potent efficacy on ulcer healing, Lansoprazole may be the drug of choice in the treatment of duodenal ulcers.

REFERENCES

1. Spencer MC, Faulds D. Lansoprazole. Drugs. 1994; 48 (3): 404-430.
2. Barradell LB, Faulds D, McTavish D. Drugs. 1992; 44 (2): 225-250.
3. Sipponen P. Helicobacter pylori, chronic gastritis and peptic ulcer. Materia Medica Polona. 1992; 3 (83):166-168.
4. Hawkey CJ, Long RG, Bardhan KD, et al. Improved symptom relief and duodenal ulcer healing with Lansoprazole, a new proton pump inhibitor, compared with Ranitidine. Gut 1993; 34: 1458-1462.
5. Lamouliatte H. Effect of Lansoprazole on Helicobacter pylori. Clin Therapeutics 1993; 15 (suppl.B): 32-37.
6. Bardhan KD, Ahlberg J, Hislop WS, et al. Rapid Healing of Gastric Ulcers with Lansoprazole. Aliment Pharmacol Ther 1994; 8: 215-220.
7. Sakita T, Omori K. The Progress of Peptic Ulcer. Japan Clinic 1964; 22: 9.
8. Des Varannes SB, Levy P, Lartigue S, et al. Comparison of Lansoprazole with Omeprazole on 24-hour Intragastric pH, Acid Secretion and Serum Gastrin in Healthy Volunteers. Aliment Pharmacol Ther. 1994; 8: 309-314.
9. Verdü EF, Fraser R, Armstrong D, et al. Effects of Omeprazole and Lansoprazole on 24-hour Intragastric pH in Helicobacter pylori-positive Volunteers. Scand J Gastroenterol. 1994; 29: 1065-4069.
10. Nagata K, Takagi E, Tsuda M, et al. Inhibitory Action of Lansoprazole and Its Analogs Against Helicobacter pylori: Inhibition of Growth Is Not Related to Inhibition of Urease. Antimicrob Agents Chemother 1993; 37: 769-774.
11. Pallone F, Luzza F. Lansoprazole and Helicobacter pylori Infection. Clin Therapeutics 1993; 15 (suppl.B): 49-57.
12. Tsuji S, Kawano S, Higashi T, et al. Gastric Ulcer Healing and Basic Fibroblast Growth Factor: Effects of Lansoprazole and Famotidine. J Clin Gastroenterol 1995; 20(suppl.2): S1-S4.
13. Suzuki M, Nakamura M, Mori M. Lansoprazole Inhibits Oxygen-Derived Free Radical Production from Neutrophils Activated by Helicobacter pylori. J Clin Gastroenterol 1995; 20(suppl.2): S93-S96.
14. Lanza F, Goff J, Scowcroft C, et al. Double-blind Comparison of Lansoprazol, Ranitidine, and Placebo in the Treatment of Acute Duodenal Ulcer. Am J Gastroenterol 1994; 89 (8): 1191-1200.
15. Petite JP, Slama JL, Licht H, et al. Comparaison du lansoprazole (30 mg) et de l'omeprazole (20mg) dans le traitement de l'ulcere duodenal. Gastroenterol Clin Biol 1993; 17: 334-340.
16. Christian F. Progress with Proton Pump Inhibitors in Acid Peptic Disease: Treatment of Duodenal and Gastric Ulcer. Clin Therapeutics 1993; 15 (suppl.B):14-20.
17. Ekström P, Carling L, Unge P, et al. Lansoprazole Versus Omeprazole in Active Duodenal Ulcer; A Double-Blind, Randomized, Comparative Study. Scand J Gastroenterol 1995; 30: 210-215.

EFFECTS OF LEVOTHYROXINE ON SERUM ANDROGEN LEVELS IN WOMEN

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SUMMARY

Endemic goiter is an important and common health problem in some countries. Most patients with endemic goiters are treated using levothyroxine (LT4). Some female patients who are under suppressive LT4 therapy show an increase in androgen-dependent body hair growth. The purpose of this study was to evaluate the effects of LT4 treatment on serum androgen levels in women. Twenty-five female patients who had euthyroid diffuse or nodular goiters were included in the study. An age-matched control group was also evaluated. None of the subjects had hirsutism or any other medical illnesses, and all were menstruating regularly. The ages of the patients were between 18 and 36 years (mean: 25yr). Both patient and control groups had normal body mass indexes (< 24 kilogram/m²). Basal serum thyrotropin (TSH), free thyroxine, free triiodothyronine, FSH, LH, estradiol, free testosterone, total testosterone, dehydroepiandrosterone sulfate (DHEAS) and 17 hydroxy-progesterone (17OH P) levels were measured at the early follicular phase of the menstrual cycle and found to be within normal ranges. Levothyroxine treatment was initiated in the patient group at a dose of 2-2.5 microgram/kg. Hormonal evaluations were repeated at the third and sixth month in both patient and control groups. Mean TSH level remained unchanged in the control group and decreased significantly in the treatment group (1.41 vs. 0.29 at three months and 0.27 at six months, p<0.001). Despite this effective suppression in TSH in patients, serum FSH, LH, estradiol, free and total testosterone, DHEAS and 17OH P levels showed no change during levothyroxine therapy, and no difference could be found between gonadotropin, estradiol or androgen levels of controls and patients. According to these results, since levothyroxine had no effect on serum androgen levels, it can be suggested that the development of hirsutism in women taking levothyroxine is not due to the drug itself. As hirsutism is a common condition in Mediterranean countries, excessive hair growth in these women could be a result of the natural course of the disease.

Key words: *Hirsutism, Levothyroxine*

ÖZET

Kadınlarda Androjen Düzeylerine Levotiroksin'in Etkileri

Endemik guatr tedavisi sıklıkla levotiroksin (LT4) ile yapılmaktadır. LT4 tedavisi altındaki kadın hastaların bazılarında androjen bağımlı kıllarda bir artış gözlenmektedir. Bu çalışmanın amacı LT4 tedavisinin kadınlarda androjen düzeylerine etkilerinin araştırılmasıdır. Difüz ya da nodüler guatrı olan, yaşların 18-36 yaş arasında (ortalama 25 yaş), 25 kadın hasta çalışmaya dahil edilmiştir. Yaşları ve beden kitle indeksleri hastalarla uyumlu, sağlıklı kadınlardan oluşan bir kontrol grubu da incelenmiştir. Hem hasta, hem de kontrol grubunda serum tirotropin (TSH), serbest T4, serbest T3, FSH, LH, estradiol, serbest testosteron, total testosteron, dehidroepiandrosteron sülfat (DHEAS) ve 17-hidroksi-progesteron (17-OH-P) seviyeleri menstrüel siklusun erken folliküler fazında değerlendirildi ve başlangıçta hepsi normal sınırlar içerisinde bulundu. Bu değerlendirmeleri takiben hasta grubuna LT4 2-2.5 mikrogram/gün dozunda başlandı. Hormonal incelemeler her iki grupta da üçüncü ve altıncı aylarda tekrarlandı. Serum TSH düzeyi kontrol grubunda çalışma süresince değişme göstermezken, LT4 grubunda anlamlı olarak düştü (1.41 IU/L'ye karşın üçüncü ayda 0.29 IU/L ve altıncı ayda 0.27, p<0.001). TSH düzeylerinde anlamlı düşmeye rağmen hastalarda LT4 tedavisi süresince serum FSH, LH, serbest ve total testosteron, estradiol, DHEAS ve 17-OH-P düzeylerinde değişim saptanamadı. Tedavi sırasında bulunan gonadotropin, estradiol ve androjen seviyeleri açısından kontrol grubu ile hastalar arasında fark yoktu. Sonuç olarak, androjen seviyelerinde tedavi süresince değişiklik olmaması nedeniyle, LT4 alan kadın hastalarda ortaya çıkan hisutizmin ilaç etkisine bağlı olmadığı söylenebilir. Hirsutizm Akdeniz ülkelerinde yaygın bir sorun olduğuna göre bu kadınlarda gözlenen kıllanma artışı hastalığın doğal seyri olarak değerlendirilmelidir.

Anahtar kelimeler: *Hirsutizm, Levotiroksin*

Hirsutism is defined as the excess of male-pattern hair growth in women (1-6) and is a common problem among Turkish women (7). Idiopathic hirsutism and polycystic ovary disease are the most common causes of hirsutism (2). Several drugs can cause excessive hair growth. Androgens, minoxidil, diazoxide, phenyto-

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in, glucocorticoids and cyclosporine are drugs known to cause hirsutism (1).

Levothyroxine suppression treatment is a well-known and accepted therapy modality in the treatment of euthyroid diffuse and nodular goiters (8,9). Thyroid hormones increase the serum concentration of sex-hormone-binding globulin (SHBG))11, 13). As a result, patients with hypothyroidism may have decreased serum SHBG and increased free testosterone (2). Therefore, hypothyroidism is accepted as a cause of hirsutism even though hyperthyroidism does not cause excessive hair growth.

Some women taking levothyroxine for their goiters complain about an increase in androgen-dependent hair growth; however, levothyroxine is not among the drugs that cause hirsutism. The aim of this study was to evaluate the effects of long-term levothyroxine suppression treatment on androgen levels in non-hirsute women.

MATERIAL AND METHODS

Twenty-five female patients who had euthyroid diffuse or nodular goiters were included in the study. An age-matched control group was also evaluated. None of the subjects had hirsutism or any other medical illnesses, and all were menstruating regularly. The ages of the patients were between 18 and 36 years (mean: 25yr). Both patient and control groups had normal body mass indexes (< 24 kilogram/m^2).

Basal serum thyrotropin (TSH), free thyroxine, free triiodothyronine, FSH, LH, estradiol, free testosterone, total testosterone, dehydroepiandrosterone sulfate (DHEAS) and 17 hydroxy-progesterone (17OH P) levels were measured at the early follicular phase of menstrual cycles.

Levothyroxine treatment was initiated in the patient group at a dose of 2-2.5 microgram/kg. The hormonal evaluations were repeated at three and six months in both patient and control groups.

Assays: Samples were analyzed in duplicate in the same assay to avoid interassay variations. Serum FSH, LH and TSH (Medgenix, Belgium) and Prolactin (Orion Diagnostica, Finland) were measured using IRMA kits. TT and FT (Diagnostic Products Corp., USA), DHEAS, 17 OH P (Diagnostic System Lab, USA) and Estradiol (Amersham, UK) determinations were made using RIA kits.

Statistical Analysis: Student's test for paired samples, two-tailed significance for comparisons and variance analysis tests were used, and .p values below 0.05 were considered to be significant. All values were reported as mean ± SD.

RESULTS

The mean basal and six-month hormonal profiles of the women are given in Table 1.

Mean baseline hormonal levels of both groups were similar with no statistically significant difference. Serum FSH, LH, estradiol, total testosterone, free testosterone, 17OH progesterone and DHEAS levels did not change in the treatment group, and no statistically significant difference was found from either baseline levels or from controls.

Table 1. Hormonal profiles of patients and controls before and after six months of levothyroxine treatment.

	Basal		6th Month		
Hormone	Patient	Control	Patient	Control	p
FSH (mIU /ml)	6.43±2.4	6.51±2.1	6.07±2.06	6.11±2.2	>0.05
LH (mIU /ml)	6.19±3.0	6.07±2.3	6.14±2.92	5.98±2.3	>0.05
E2 (pg/ml)	58±17	55±21	54±18	59±20	>0.05
TT(ng/dl)	73±40	68±34	60±28	65±37	>0.05
FT (pg/ml)	2.7±1.2	3.1±1.1	3.1±2.4	2.9±2.5	>0.05
DHEAS (m g/dl)	263±212	248±247	276±150	267±168	>0.05
17OHP(nmol/L)	1.23±0.65	1.35±1.3	1.36±0.67	1.44±1.1	>0.05
TSH (m U/ml)	1.41±0.69*	1.29±0.9	0.27±0.31*	1.4±0.7	<0.001

* Results are given as mean±SD

TT: Total Testosterone, FT: Free Testosterone

The mean TSH level remained unchanged in the control group and decreased significantly in the treatment group (1.41 mIU/ml vs. 0.27 mIU/ml at six months, $p<0.001$).

DISCUSSION

In the present study, serum FSH, LH, estradiol, free and total testosterone, DHEAS and 17OH P levels did not change during six months of levothyroxine therapy despite effective suppression of TSH in patients.

Studies on the effects of levothyroxine on serum androgen levels are conflicting. Belgorosky et al (11) found no change in total testosterone or estradiol levels after levothyroxine treatment, but they observed a significant decrease in DHEAS levels. Koloğlu et al (7) found decreased levels of SHBG and increased levels of DHEAS in their patients taking levothyroxine for at least six months.

In hyperthyroid patients, Ford et al (12) found an increase in SHBG levels and a decrease in non-SHBG-bound and free testosterone levels. Giagulli and Vermeulen (13) found an increase in SHBG but no change in DHEAS levels.

Some but not all women complain of hirsutism while undergoing levothyroxine treatment. It is known that increased conversion from vellus to terminal hairs is caused by either an increased sensitivity of the hair follicle to normal levels of androgens, increased 5 alpha reductase activity or increased androgen production by the endocrine glands (1). Two possible explanations may be given for the connection between hirsutism and levothyroxine. First, it is possible that while study serum androgen levels do not increase with levothyroxine, there is an increased sensitivity of the hair follicle to these normal, unchanged levels. Second, it is possible that, since the duration of exposure to androgens is an important variable in the development of hirsutism, some women may develop excessive hair growth as a result of the natural courses of their diseases.

In conclusion, treatment with levothyroxine does not alter the androgen levels in non-hirsute women. Still, it is a fact that some women complain of the development of hirsutism when using the drug. Further studies need to be carried out to evaluate the effects of levothyroxine on hair follicles, since an increased sensitivity to androgens may play a role in the development of excessive hair growth, especially in connection with long-term use of levothyroxine.

REFERENCES

1. Rittmaster RS, Loriaux L. Hirsutism. Ann Intern Med; 106: 95-107, 1987.
2. Leung AKC. Hirsutism. Int J Dermatol; 32:773-777, 1993.
3. Goldfien A, Monroe SE. Hirsutism. In Basic and clinical endocrinology, Greenspan FS & Strewler GJ eds., 5th edition, Prentice-Hall International Inc 1997, pp 463-468.
4. Carr BR. Hirsutism and virilism. In Williams Textbook of Endocrinology, Wilson JD and Foster DW eds, 8th edition, WB Saunders Company, 1992, pp 776-780.
5. Delahunt JW. Hirsutism. Practical Therapeutic Guidelines. Drugs; 45:223-231, 1993.
6. Rittmaster RS. Medical Treatment of Androgen-Dependent Hirsutism. J Clin Endocrinol Metab; 80:2559-2563, 1995.
7. Koloğlu S, Başkal N, Koloğlu LB, Laleli Y, Tüccar E. Hirsutism due to the treatment with L-thyroxine in patients with thyroid pathology. Rev Roum Med; 26:179-185, 1988.
8. Perrild H, Hansen JM, Hegedus L, Rytter L, Holm B, Gundtofte E, Johansen K. Triiodothyronine and thyroxine treatment of diffuse non-toxic goiter evaluated by ultrasonic scanning. Acta Endocrinol (Copenh); 100:382-387, 1982.
9. Burch HB. Evaluation and management of the solid thyroid nodule. Endocrinol Metab Clin North America; 24:663-710, 1995.
10. Natrajan PK. Hirsutism and the endocrine system. In The cause and management of Hirsutism. Greenblatt RB, Mahesh VB and Gambrell RD eds. The Parthenon Publishing Group, 1987, pp 45-60
11. Belgorosky A, Kaplan J, Cardoso E, Hoschoian JC, Rivarola MA. Changes in the distribution of testosterone and estradiol serum fractions in hirsute women after administration of L-thyroxine. Medicina; 49:331-335, 1989.
12. Ford HC, Cooke RR, Keightley EA, Feek CM. Serum levels of free and bound testosterone in hyperthyroidism. Clin Endocrinol; 36:187-192, 1992.
13. Giagulli VA, Vermeulen A. Increased plasma 5 alpha-androstane-3 alpha, 17 beta-diol glucuronide concentration in clinically euthyroid women with suppressed plasma thyrotropin levels: further evidence for generalized tissue overexposure to thyroid hormones in these subjects. J Cli Endocrinol Metab; 74:1465-1467,1992.

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GRADES OF CLINICALLY SALT-LOSING IN THE PATIENTS WITH 21-HYDROXYLASE DEFICIENCY

Gönül Öcal • Merih Berberoğlu • Ergun Çetinkaya • Pelin Adıyaman • Ercan Tutar

SUMMARY

Classic congenital adrenal hyperplasia due to a 21-hydroxylase deficiency (21OHD) is classified as a salt loss inducing and simple-virilizing form, depending on the symptoms at the time of diagnosis. Patients with clinical signs of salt loss and/or with hyponatremia, hyperpotassemia, and elevated plasma renin activity (PRA), are considered to have the salt loss inducing form of 21OHD. However, this group of patients is not homogenous in terms of their aldosterone secretion capacity. A number of subjects may show high aldosterone concentrations, instead of a mineral corticoid deficiency.

In this study, 41 children with classic cases of 21OHD were evaluated for a clinical spectrum of salt wasting and biochemical features (cortisol, 17OHP, aldosterone, PRA, serum sodium and potassium). In the initial analysis, the results were divided into 2 groups according to their serum electrolyte levels. Group I was made up of those with the salt loss inducing form (Na < 130 mEq/L ,K > 6 mEq/L); group II was considered those with the simple virilizing form of 21OHD, initially. These groups were sub grouped according to their serum aldosterone concentrations (above or below 125 pgr/ml). Among 41 patients who participated in this study, 12 had severe salt loss and aldosterone deficiency, 8 had partially compensated moderate salt loss with hyperreninemia and hyperaldosteronemia, 10 had compensated mild salt loss, and 11 had no clinical and biochemical sodium loss with normoreninemia and normoaldosteronemia. All forms of 21OHD, including the simple virilizing form and with the exception of those in Group IIa, showed some evidence of sodium loss. Plasma renin activity may be raised in children who have never had clinical salt loss episodes and electrolyte imbalance (Group IIa) .

In conclusion, sodium loss in 21OHD is a graded phenomenon. The definition of the salt loss inducing and simple virilization form of 21OHD is divided into arbitrary categories.

Keywords: *Congenital adrenal hyperplasia, 21-hydroxylase deficiency*

ÖZET

21-Hidroksilaz Eksikliğinde Klinik Tuz Kaybı Değerlendirilmesi

21-Hidroksilaz eksikliğine bağlı klasik konjenital adrenal hiperplazinin; tanı esnasındaki semptomlara bağlı olarak tuz yitiren formu ve basit-virilizan formları mevcuttur. Klinik olarak tuz yitme bulguları ve/veya hiponatremi, hiperpotasemi, hiperreninemi bulgularının olması 21-Hidroksilaz eksikliğinin tuz yitiren formu olarak kabul edilir. Ancak, bu grup hastalar aldosteron sekresyon kapasiteleri açısından homojen değildirler. Bazı vakalarda mineralokortikoid eksikliği olmadan yüksek aldosteron konsantrasyonları görülebilmektedir.

Bu çalışmada klasik 21-Hidroksilaz eksikliği olan 41 olgu incelendi ve tuz yitme bulguları ile biokimyasal bulguları (kortizol, 17OHP, aldosteron, PRA, serum NA^+ ve K^+) değerlendirildi. Başlangıçta serum elektrolit değerlerine göre hastalar 2 gruba ayrıldı. Grup I, tuz yitiren grup iken (Na<130 mEq/L, K>6 mEq/L), Grup II basit virilizan formu oluşturdu. Bu gruplar serum aldosteron düzeylerine göre kendi içlerinde subgruplara ayrıldı (125 pgr/ml'nin üstünde veya altında olanlar olarak). Kırkbir olgudan 12'sinde ciddi tuz kaybı ve aldosteron eksikliği, 8'inde hiperreninemi ve hiperaldosteronemi ile birlikte kısmen kompanse orta derecede tuz kaybı, 10'unda ise hafif kompanse tuz kaybı varken, 11 olguda normoreninemi ve normoaldosteronemi ile klinik ve biokimyasal tuz kaybı saptanmadı. Grup IIa haricinde, basit virilizan formlar da dahil olmak üzere 21-Hidroksilaz eksikliğinin tüm formlarında tuz kaybı mevcuttu. Grup IIa'da olduğu gibi hiçbir tuz kaybı ve elektrolit imbalansı olmayan hastalarda yüksek düzeylerde plasma renin aktivitesi saptanabileceği görüldü.

Sonuç olarak; 21-Hidroksilaz eksikliğinde tuz kaybı önemli bir olay olup, 21-Hidroksilaz eksikliğinin tuz yitiren ve basit virilizan formlarının tanımları değişkenlik gösterebilmektedir.

Anahtar kelimeler: *Kongenital adrenal hiperplazi, 21-hidroksilaz eksikliği*

Classic congenital adrenal hyperplasia, due to 21-hydroxylase deficiency (21OHD), is classified as a salt loss inducing and simple virilizing type, depending on the symptoms at the time of diagnosis. These cases represent points on a continuous spectrum of disease severity (1,2). Renal salt wasting due to aldosterone

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deficiency is usually considered as the cause in three fourths of these cases. However, some doubt remains about this as the cause and question if the frequency of aldosterone deficiency in these patients is as high as generally thought. Patients with clinical signs of salt loss and/or with hyponatremia, hyperpotassemia and increased plasma renin activity (PRA) are considered to have the salt loss inducing form of 21OHD. This group of patients, however, is not homogenous for aldosterone secretion capacity (3-9).

In this study, we evaluated the clinical and biochemical spectrum of salt loss in 41 patients with classical 21OHD. The aim of the present study was to document the pattern of abnormalities in the sodium balance in our patients in order to determine the best means for therapeutic management.

METHODS

Selection of Patients: Forty-one patients (14 genetic males, 27 genetic females), aged newborn to 9 years old (mean 2.4 (2 years) were studied. A diagnosis of 21OHD was based on typical clinical signs and/or symptoms (virilization, accelerated growth with or without salt loss) and elevated morning 17-alfa hydroxyprogesterone (17OHP) levels. Women with the virilized form had an enlargement of the clitoris and a variable degree of labio-scrotal fusion. In some extreme cases, the fusion was so extensive that the external genitalia were mistaken for those of a cryptorchidic male.

The diagnostic procedure also included a determination of the genetic sex by karyotyping, bone age assessment, plasma sodium and potassium measurement, and hormonal determination (morning cortisol, ACTH, plasma renin activity, aldosterone and DHEA/S) by RIA using commercially available kits. The results of testing PRA and aldosterone and cortisol levels were compared with that of the 14 healthy nonhypertensive controls in the same age groups. (PRA 0.8±0.2 ng/ml/hr, Aldosterone 87±15 pg/ml, Cortisol 15.3±6 m g/dl).

Study design: Initially the patients were divided into two groups, according to their serum sodium and potassium concentrations. Group I (Sodium < 130 mEq/l, potassium > 6 mEq/l) and Group II (Sodium > 130 mEq/l, potassium < 6 mEq/l). These groups were later sub grouped according to their aldosterone values as compared with the control values (Group Ia-Ib and Group IIa-IIb).

The studentís t-test was performed to compare the biochemical findings (serum sodium, potassium, PRA, aldosterone, cortisol) of the groups. The results were expressed as a mean ± SD.

RESULTS

The clinical and biochemical spectrum of salt loss and the hormonal features of 41 patients with classical 21 OHD are outlined in Table 1. The distribution of the patients for the degree of salt loss is shown in Figure 1.

Initially, according to their clinical features and electrolyte levels, Group I was considered as those with the salt loss inducing form and Group II was considered as those with the simple virilizing form of 21-hydroxylase deficiency. But real mineral corticoid secretion deficiency and complete 21OHD was found in Group Ia (29.2 percent of 41 patients). Although none of our patients, except those in Group Ia, showed clinical signs of sodium depletion upon admission, various abnormalities in PRA and aldosterone values were documented in most of them. Increased PRA, associated with the wide spectrum of serum aldosterone levels, was documented in Group Ia,Ib and IIa.

In all, 41 patients with 21OHD participated in the study. Twelve had uncompensated severe salt loss with spontaneous salt wasting crises, severe hyponatremia (118±8.6 mEq/l), hyperpotassemia (7.34±1.07 mEq/l), hyperreninemia (41.06±24 ng/ml/hr), and low morning cortisol levels (3.33±1.5 (g/dl). Eight had partially compensated, moderate salt loss with stress induced salt depletion crises, moderate hyponatremia (127±2 mEq/l), hyperpotassemia (6.8±0.3 mEq/l), hyperreninemia (22.6±10 ng /ml/hr), hyperaldosteronemia (1072±600 pg/ml), and low or low normal morning cortisol values (9.98±7 m g/dl). Ten had compensated mild salt loss with unnoticeable clinical sodium depletion, normonatremia (139.2±3.1 mEq/l), normopotasemia (3.8±0.6 meq/l), hyperreninemia (29.8±21

Table 1. Clinical and Biochemical data in subjects with 21OHD

Subgroups of Patients with 21 OHD		Clinical Salt Loss	Sodium mEq/l	Potassium mEq/l	PRA** ng/ml/hr	Aldosterone pg/ml	Cortisol mcg/dL
GRP I Na<130mEq/L K>6 mEq/L	IA (n=12) (uncompensated severe SW*)	Spontaneus	118 ± 8.6	7.34 ± 1.07	41.06 ± 24	21.09 ± 10	3.33 ± 1.52
	IB (n=8) (Nearly compensated moderate SW)	with Stress	127.7 ± 2	6.8 ± 0.3	22.6 ± 10	1072 ± 600	9.98 ± 7
GRP II Na>130 mEq/L K<6 mEq/L	IIA (n=10) (Compensated mild SW	Absent	139.2 ± 3.1	3.8 ± 0.6	29.8 ± 21	795 ± 200	12.3 ± 6.2
	IIB (n=11) Simple virilizing	Absent	138.9 ± 4	4.2 ± 0.6	1.94 ± 1.4	114.8 ± 8	9.8 ± 1.8
Results expressed mean ± SD							
		Significance	a,b,d,e,f	b,d,e,f	a,c,e,f	a,c,d,e,f	a,d,e
		a: Group IA vs IB p<0.05	b: Group IB vs IIA p<0.05	c: Group IIA vs IIB p<0.05	d: Group IIA vs IIB p<0.05	E: Group IIA vs IIB p<0.05	F: Group IIA vs IIB p<0.05

* SW: Salt-wasting
**PRA: Plasma renin activity

ng/ml/hr), hyperaldosteronemia (795±20 pg/ml), and normal morning cortisol values (12.3±6.2 (g/dl). Eleven had no clinical signs of sodium depletion, normonatremia (138.9±4 mEq/l), normopotasemia (4.2±0.6 mEq/l), normoreninemia (1.94±1.4 ng/ml/hr), higher than normal aldosterone levels (114±8 pg/ml), and low normal morning cortisol values (9.8±1.8 m g/dl).

DISCUSSION

The classical 21-hydroxylase deficiency should be considered a single disorder with a wide spectrum of clinical manifestations related to sodium conservation, instead of two separate disorders known as the sodium loss inducing and non-sodium loss inducing forms. The clinical spectrum of 21OHD varies throughout life and within the individual (17).

There is no single, simple correct regimen in the treatment of 21-hydroxylase deficiency, so management must be individualized for each patient (10). At this point, a determination of the grades of sodium depletion is very important. Mild chronic compensated hypovolemia caused by mild degrees of mineral

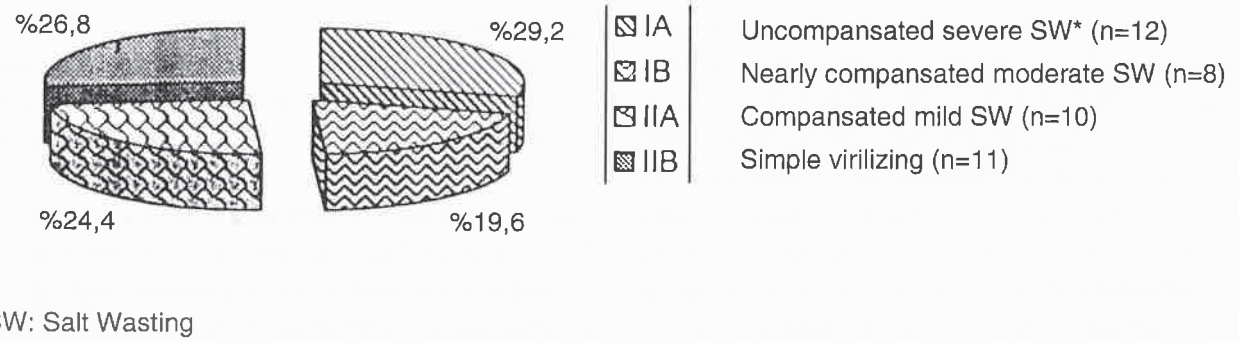

Figure 1: Distribution of patients for salt-losing spectrum

corticoid deficiency in those patients considered to have the simple virilizing type, could not be corrected by glucocorticoid replacement alone. Over or under treatment with glucocorticoids results in poor growth (1,2,7,10-12). On the other hand, a number of subjects, who exhibit severe salt-losing tendency at birth, can develop significant hypertension on standard mineral corticoid therapy (3).

Patients with 21OHD are known to suffer from the same basic enzyme malfunction, but their clinical pictures may be very different (1,2). Wilson et al. pointed out that the 10 most common mutations observed in the 21-hydroxylase-gene result in phenotypes that are not always concordant with the genotypes (13). The accepted knowledge that a patient with CAH is homozygous for a defective 21-B gene is not strictly true (1,2,13). Patients, who are homozygously effected due to a compound heterozygous gene, have inherited a different mutation in each P450c21 allele (2).

The presence of mild mineral corticoid deficiency in clinically non-salt inducing patients is should be noted as very important for the successful management of the disease. Most of our subjects displayed varying degrees of sodium depletion, which did not always clinically manifest themselves, as mentioned previously (1-6,14).

Compensated and uncompensated sodium loss occurred in 73.13 % of our patients with 21OHD, but only 29.2 % of them demonstrated overt salt loss and severe aldosterone deficiency. It should be noted that the distinction between the simple virilizing and salt loss inducing phenotypes is not absolute. Initially, we considered that Group I was the salt-loss inducing type; Group II was the simple virilizing type of 21OHD. In Group Ia, aldosterone levels were inappropriately low for the degree of salt depletion as indicated by the spontaneous clinical findings of salt loss. Group Ib and IIa exhibited high aldosterone and PRA values with normal blood pressure, which were due to a tendency to salt loss without clinical appearances. Eleven of our 41 patients with 21 OHD (Group IIb, 26.8 %) were considered of the real simple virilizing type with normal PRA and aldosterone concentrations. Mineral corticoid replacement in these groups may result in hypertension, so the decision for this type of treatment must be made with caution (15).

These findings are consistent with previous observations that plasma aldosterone concentrations may be normal or even elevated in cases of salt loss CAH (1,2,5,13). Mild (with normonatremia, normopotasemia, hyperreninemia) to moderate (with low normal sodium, upper normal or high potassium, hyperreninemia) sodium loss occurs in the presence of increased aldosterone production. Mild degrees of mineral corticoid deficiency lead to the increased activity of the renin-angiotensine system (1,2,4,5,7,16,17). Increased plasma renin activity in patients clinically considered to have the simple virilizing form of 21OHD is used to assess the subtle evidence of mineral corticoid deficiency (18,19).

Serum cortisol levels are low in our patients with the severe salt losing type, but close to normal in compensated salt wasting (mild to moderate) and real simple virilizing types. Individuals who had a severe form of the disorder (Group Ia) showed significant degrees of sodium depletion and electrolyte abnormalities with a marked impairment of aldosterone and cortisol secretion, as expected. Morning cortisol levels of other groups (Ib,IIa,IIb) were ranged in low normal-to-normal values.

It is well known that the adrenal gland normally produces 100 to 1000 times as much cortisol as aldosterone, so that mild defects in P450c21 are much less likely to affect mineral corticoid secretion than cortisol secretion (2,9). It appears that as little as 1% of normal activity allows nearly adequate aldosterone synthesis to prevent significant salt loss. White et al. suggested that the difference between the simple virilizing and the salt loss inducing phenotypes is essentially a quantitative difference in activity (9). Thus, patients with a simple virilizing 21-hydroxylase deficiency, without elevated PRA, have a less severe mutation in the functional P450c21 gene.

In conclusion, the definitions of the salt loss inducing and simple virilizing forms of 21OHD are arbitrary categories. There is no distinct difference between these two forms of 21OHD. Salt loss should not be used as a synonym for aldosterone deficiency. Sodium loss is a graded phenomenon in these patients with the following distinctions: compensated mild salt loss; nearly compensated moderate salt loss and uncompensated severe salt loss.

REFERENCES

1. Miller WL: Clinical Review 54.Genetics, Diagnosis and Management of 21-hydroxylase deficiency. J Clin Endocrinol Metab 78:241-46 ,1994.
2. Miller WL: Pathophysiology, Genetics and Treatment of hyperandrogenism Ped Clin North Amer. 44:375-96 ,1997.
3. Keenan B.S, Holcombe J.H, K1rkland R.T, Potts VE. And Clayton GW: Sodium homeostasis and aldosterone secretion in salt-losing congenital adrenal hyperplasia. J Clin Endocrinol Metab 48:430-4, 1979.
4. Rosler A, Levine L.S, Schneider B et al. The interrelationship of sodium balance, plasma renin activity and ACTH in CAH. J Clin Endocrinol Metab 70:229-33, 1977.
5. Horner J.M, Hintz R.L, Luztscher J.A: The role of renin and angiotensin in salt-losing 21-hydroxylase deficient congenital adrenal hyperplasia. J Clin Endocrinol Metab 48:776, 1979.
6. Holcombe J.H, Keenan B.S, Clayton G.W, Kumar S: Role of salt-losing hormones in congenital adrenal hyperplasia. J Pediatr 98:573-75, 1981.
7. Griffiths K.D, Anderson J.M, Rudd B.T: Plasma renin activity in the management of congenital adrenal hyperplasia. Arch Dis Child 59:360, 1984.
8. Speiser P.W, Agdere L, Ueshiba H et al. Aldosterone synthesis in salt wasting congenital adrenal hyperplasia with complete absence of adrenal 21-hydroxylase New Engl J Med 324:145-149, 1991.
9. White P.C., New M.I : Genetic basis of endocrine disease. congenital adrenal hyperplasia due to 21 hydroxylase deficiency. J Clin Endocrinol 74:6-11, 1992.
10. Sandrini R, Jospe N, and Migeon C.J: Temporal and individual variation in the dose of glucocorticoid used for the treatment of salt-losing congenital virilizing adrenal hyperplasia due to 21-hydroxylase deficiency. Acta Pediatr Suppl. 388:56-60, 1993.
11. New M.I, Gertner J.M, Chir B, Speiser P.W, Balao P: Growth and final height in classic and nonclassic 21-hydroxylase deficiency. Acta Pediatr Jpn. 30 (suppl) 79-88, 1988.
12. Knorr D, H1nrichsen S.G.C: Persistent obesity and short final height after over- treatment for congenital adrenal hyperplasia in infancy. Acta Pediatr Jpn. 30 (suppl) 89-92, 1988.
13. Wilson R.C, Mercado A.B, Cheng K.C, New M.I: Steroid 21-hydroxylase deficiency. Genotype may not predict phenotype. J Clin Endocrinol Metab 80. 2322-29, 1995.
14. Siegel S.F, Lee P.A, Adrenal cortex and medulla from clinical endocrinology Ed. Hung W: Mosby Year Book Inc. Boston 179-225, 1992.
15. Kirkland J.L, Kirkland L, Librik L, and Clayton G.W: Iatrogenic hypertension in children with congenital adrenal hyperplasia. J Pediatr 83: 687,1973.
16. Simopoulous A.P, Marshal J.K, Delea C.S et al: Studies on the deficiency of 21-hydroxylation in patients with congenital adrenal hyperplasia. J Clin Endocrinol Metab 32:438-443, 1971.
17. Lipton H.L, Tan S.Y, North R, Mulrow P.J, Genel M: Usefulness of PRA to monitor mineral corticoid replacement in salt-losing congenital adrenal hyperplasia In Lee P.A, Plotnick L.P, Kowarsky A.A, Migeon C.J Editors: Congenital adrenal hyperplasia Park Press Baltimore: 127-139, 1977.
18. Prader A: Pediatric Endocrinology: Past and future from pediatric endocrinology Past and Future. Ed by Ranke M.B and Bierich J.R: M.D Verlag, Munchen, pp 13-21, 1986.
19. Dorr H.G: Diagnosis and treatment of congenital adrenal hyperplasia due to 21-hydroxylase deficiency. Highlights (Novocare) 5:8-12, 1998.

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MICROSURGICAL ANATOMY OF THE INTRACRANIAL COURSE OF THE TROCHLEAR NERVE*

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Erdener Timurkaynak** • Hasan Ozan****

SUMMARY

In this study, 32 trochlear nerves from 16 cadaver heads fixed in formalin were examined in micro anatomical detail. The course of the nerve after the exit from the brain stem and its relationship with the tentorial incisura, the infratentorial, the intracavernous and the intraorbital portions of this nerve were studied. The neural and vascular relationships of each part were examined and measurements were taken. The mean total length of the trochlear nerve from the point of origin to its entrance in the superior oblique muscle was 79.1 mm. The mean diameter of the trochlear nerve, at the entrance point into the free edge of tentorium, was 0.74 mm. The mean length of the infratentorial part, intra cavernous part and the intra orbital part of the trochlear nerve were 32.1 mm, 24.4 mm, and 22.6 mm respectively. The course of the nerve, and its relation to the adjacent structures and pathological situations which involve these structures, were discussed in this study.

Keywords: *Anatomy, microsurgery, trochlear nerve*

ÖZET

Troklear Sinirin İntrakranial Yolunun Mikrocerrahi Anatomisi

Bu çalışmada, formalin ile fikse edilmiş olan 16 kadavrada, 32 troklear sinir mikroanatomik detaylarıyla incelenmiştir. Sinirin beyin sapından çıktıktan sonra izlediği rota, tentorial insisura ile olan ilişkisi, infratentorial, intrakavernöz ve intraorbital kısımları çalışılmıştır. Herbir kısmın nöral ve vasküler ilişkileri incelenmiş ve bazı ölçümler yapılmıştır. Troklear sinirin orijininden superior oblik kasın insersiyosuna kadar olan ortalama total uzunluğu 79.1 mm. olarak bulunmuştur. Troklear sinirin ortalama çapı, tentoriumun serbest kenarına girdiği yerde 0.74 mm olarak bulunmuştur. İnfratentorial, intrakavernöz ve intraorbital kısımların ortalama uzunlukları sırasıyla 32.1 mm., 24.4 mm. ve 22.6 mm. olarak bulunmuştur. Troklear sinirin bütün seyri boyunca komşu yapılarla olan ilişkileri ve bu yapıların neden olduğu patolojiler tartışılmıştır.

Anahtar kelimeler: *Anatomi, mikrocerrahi, troklear sinir*

The trochlear nerve is the most slender of the cranial nerves, and it has the longest intracranial course of all the cranial nerves. It supplies the superior oblique muscle. The trochlear nerve arises below the inferior colliculus in the posterior incisural space and runs round the lateral aspect of the midbrain infratentorially to enter the cavernous sinus (1). It is the only cranial nerve to exit the brain stem dorsally (2). The oculomotor, the trochlear nerves, and the first and second divisions of the trigeminal nerve lie between the two layers of dura forming the lateral wall of the cavernous sinus (3). The trochlear nerve traverses the superior orbital fissure and ends in the orbit on the superior oblique muscle.

Contusions of the trochlear nerve against the edge of tentorium result from the acceleration and deceleration of the head and the subsequent fluid movement of the brain. The most common cause of fourth nerve palsy is trauma. Within the cavernous sinus and orbital fissure, this nerve is rarely involved as an isolated cranial nerve (2). Those patients with a traumatic fourth nerve lesion have a better prognosis than those with the other injuries to other nerves ;closed head trauma is seen more frequently in cases of trochlear nerve paralysis, whereas more forcible trauma usually causes skull fracture resulting in third and sixth nerve palsies (4).

Harris and Rhoton (5) and, more recently, Rhoton, et al (6) and Lang (7), in their descriptions of the cavernous sinus and related regions, recognized two "dural leaves" in the lateral wall of the sinus, and described the course and relationships of the nerves. The pione-

* This study was presented in part in 1998 at the 12th Scientific Congress of the Turkish Neurosurgical Society.

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ering efforts of Parkinson (8) and Dolenc et al. (9,10) have led to a variety of surgical approaches into the cavernous sinus. The surgical management of lesions involving the cavernous sinus has become routine in many neurosurgical centers. Despite improvement in the mortality rates in patients having cavernous sinus surgery, cranial nerve morbidity rates remain high (9,10,11). Even with the preservation of the anatomic continuity of the intracavernous cranial nerves, postoperative deficits are common. To reduce the incidence of cranial neuropathy, the surgeon must minimize mechanical trauma to the nerves, avoid heat injury, especially when using the laser or the bipolar coagulator, and preserve the blood supply to the cranial nerves (12).

While performing operations of intracavernous lesions, the protection of the trochlear nerve function is imperative. However, it may be difficult to preserve this nerve during the surgery because of its long course and very thin structure. Nevertheless, this nerve is ideal for reconstruction. Since it innervates a single muscle, recovery without aberrant regeneration might be expected (13). Grimson at al. (14) reported the successful recovery of the trochlear nerve function after suture.

An understanding of the microanatomy of the trochlear nerve is important in order to protect this nerve during intracranial and intraorbital surgery. In this study, the microsurgical anatomy of the trochlear nerve, its relation to adjacent structures, and anatomic variations were examined.

MATERIALS AND METHODS

32 trochlear nerves from 16 cadaver heads (specimens) fixed in formalin were dissected to examine in detail the intracranial course of the trochlear nerve. The vascular structures were perfused with colored latex to facilitate their definition. We perfused the arteries and veins once under pressure. This was performed, for example, by perfusing one carotid artery while clamping the contra lateral carotid and both vertebral arteries. 24 hours after the injections, the cadaver heads were ready for dissection. Measurements of the different sections of the nerve were taken. The relationship between the trochlear nerve and the adjacent structures was examined. During this study, the heads were fixed with a head holder and the cranium and the orbits were opened. The specimens were examined and dissected under x3 to 40 magnification provided by the Zeiss operating microscope.

RESULTS

The fourth cranial nerve has a long course, hence, three parts of the nerve could be distinguished: The infratentorial, the intracavernous, and the intraorbital. The mean total length of the trochlear nerve was 79.1 mm. The diameter of the trochlear nerve at the entrance point into the free edge of tentorium was, on average, 0.74 mm (range 0.70 to 0.96 mm).

The Infratentorial section: The trochlear nerve arises below the inferior colliculus in the posterior incisural space and passes forward through the middle incisural space (Figure 1). Its initial course around the midbrain is medial to the free edge of the tentorium in the space between the tectum and the cerebellum. The mean distance between the origins of the two trochlear nerves was 7 mm (range 4.6 to 9.4 mm.). It reaches the lower margin of the free edge of the tentorium at the posterior edge of the cerebral peduncle.

In our study, all of the 32 trochlear nerves were under the plane of the incisura tentorii. In the infratentorial part, the trochlear nerve crosses the subarachnoid cisterns, especially the ambient and quadrigeminal cisterns. It also has a close relationship with the supe-

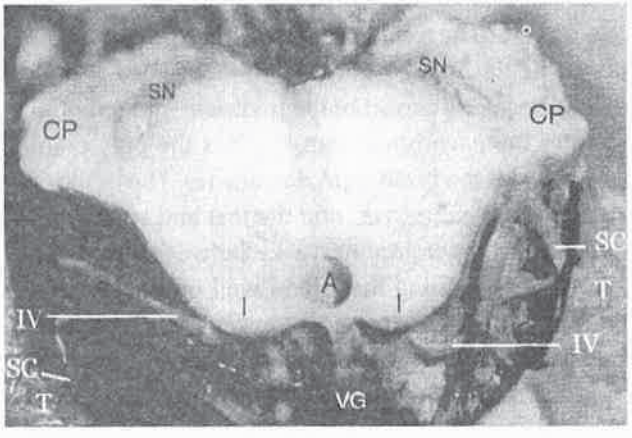

Figure 1: Superior view of the 2 trochlear nerves after the removal the cerebral hemispheres and the section of the brain stem just above the inferior colliculus; exposing their exits from the brain stem and relationship with the superior cerebellar artery. SN= substantia nigra; CP= cerebral peduncle; SC= superior cerebellar artery; I= inferior colliculus; IV= trochlear nerve; VG= vein of Galen; T= tentorium cerebelli; A= aquaductus Sylvie.

rior cerebellar artery. The 23 trochlear nerves cross the superior cerebellar artery or its collaterals at least once (71%). We usually found the trochlear nerve under the superior cerebellar artery (69 %), in 16 cases out of 23. In this part, the trochlear nerve also has a close relationship with the cerebellum and the cerebral peduncle. After its entrance into the middle incisural space, the trochlear nerve runs anteriorly, close to the free border of the tentorium cerebella, and makes a curve with a medial concavity; it then takes a sagittal direction and runs in the direction of the cavernous sinus (Figure 2). The trochlear nerve enters the roof of the cavernous sinus posterolaterally to the oculomotor nerve. The entrance point into the free edge of the tentorium was variable for each nerve. At the entrance point into the free edge of tentorium cerebella, the fourth nerve has a mean distance of 7.9 mm (range 4.4 to 12.1 mm) with the third nerve, 5.7 mm (range 3.1 to 11.7 mm) with the fifth nerve. The total length of the infratentorial part of the trochlear nerve was 32.1 mm (range 26.3 to 36.7 mm). The mean diameter of the trochlear nerve, at the entrance point into the free edge of the tentorium, was 0.74 mm (range 0.70 to 0.96 mm).

The Intracavernous section: The trochlear nerve enters the roof of the cavernous sinus posterolaterally to the oculomotor nerve and below and medial to the free edge of the tentorium (3). The trochlear and oculomotor nerves, and the first and second divisions of the trigeminal nerve, lie between the two layers of dura forming the lateral wall of the sinus.

The trochlear and the oculomotor nerves were closely approximated and run together within the cavernous sinus. The mean length of the intracavernous part of the trochlear nerve in our study was 24.4 mm (range 17 to 28.3 mm). In six cases, some connecting nerve fibers were found between the trochlear nerve and the ophthalmic nerve inside the sinus. Because of its long and very thin structure, it may be difficult to preserve the nerve during cavernous sinus surgery (Figure 3).

The fourth cranial nerve enters the orbit through the superior orbital fissure lateral to the common annular tendon and passing the superomedial margin of the frontal nerve. Its course is outside the muscle cone, and it crosses the third nerve and the optic nerve. In the region of the common annular tendon, the fourth nerve is tightly attached to the tendons; it courses in a tunnel of tendon tissue superomedially. In our study, the passage through the superior orbital fissure was approximately similar in 26 trochlear nerves. In six cases, it was just superior to the frontal nerve (Figures 3, 4 and 5).

Intraorbital section: As it enters into the orbit through the superior orbital fissure, its course becomes superior to all nerves. In the orbit, the trochlear nerve passes inward, below the origin of the levator palpebrae muscle and above the lesser wing of the sphenoid

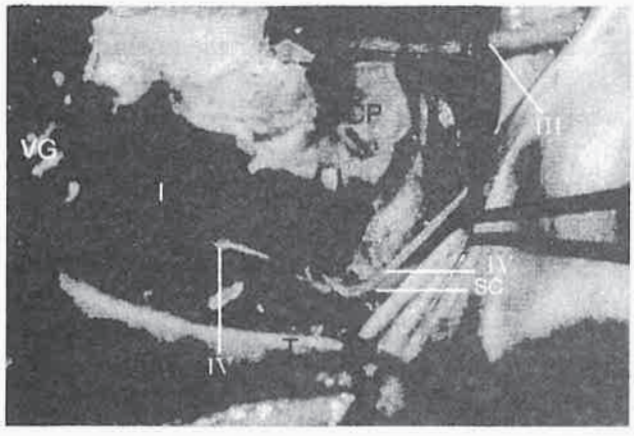

Figure 2: Superolateral view of infratentorial part of trochlear nerve after the retraction of tentorium cerebelli. Close relationship with the superior cerebellar artery, the free edge of tentorium cerebelli and oculomotor nerve are seen. VG= vein of Galen; CP= cerebral peduncle; III= oculomotor nerve; IV= trochlear nerve; SC= superior cerebellar artery; T= tentorium cerebelli.

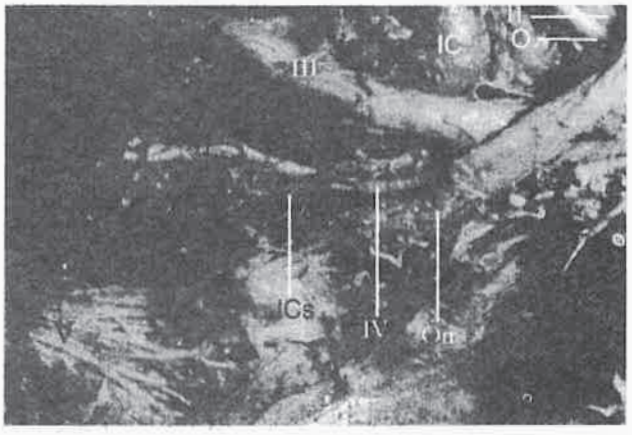

Figure 3: Lateral wall of the right cavernous sinus was opened and the trochlear nerve is seen below the oculomotor nerve in the sinus. O= ophthalmic artery; On= ophthalmic nerve; V= trigeminal nerve; IC= internal carotid artery; ICs= inferior cavernous sinus artery; IV= trochlear nerve; II= optic nerve; III= oculomotor nerve.

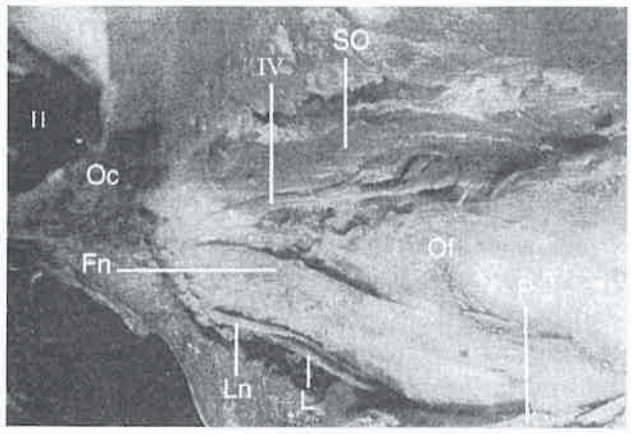

Figure 4: The photograph, showing the intraorbital part of the trochlear nerve and its entrance into the superior oblique muscle in the right orbit. The orbital roof has been removed, the periorbita opened. Of= orbital fat tissue; SO= superior oblique muscle; Oc= optic canal; Fn= frontal nerve; Ln= lacrimal nerve; P= periorbita; IV= trochlear nerve; L= lacrimal artery; II= optic nerve.

bone. The trochlear nerve was separated from the sphenoid bone only by the periosteum. Finally, it enters into the orbital surface of the superior oblique muscle (Figure 4). Its entrance into the muscle shows some variations. In 20 nerves, it separated into two branches before the entrance and in 12 nerves it separated into three branches. The mean length of the intraorbital part of the trochlear nerve was 22.6 mm (range 16 to 31.5 mm) (Figure 5). In our study, the trochlear nerve termination at the superior oblique muscle was on the medial aspect in 28 cases and on the superior edge in four cases.

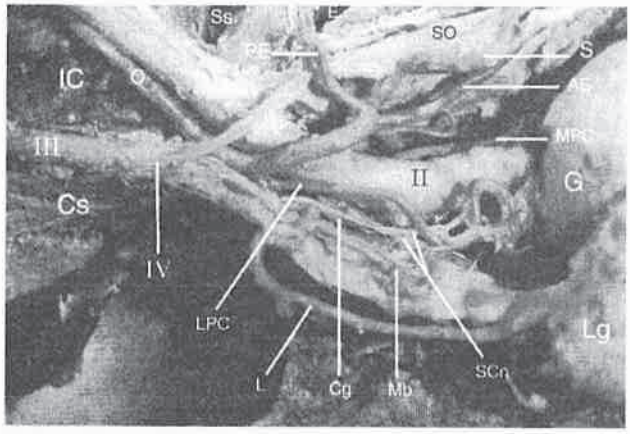

Figure 5: Intraorbital neural and vascular relationships are seen after the removal of intraorbital fat tissue. II= optic nerve; III= oculomotor nerve; IV= trochlear nerve; IC= internal carotid artery; G= globe; SO= superior oblique muscle; O= ophthalmic artery; PE= posterior ethmoidal artery; AE= anterior ethmoidal artery; L= lacrimal artery; Lg= lacrimal gland; Cg= ciliary ganglion; SCn= short ciliary nerve; Cs= cavernous sinus; LPC= lateral posterior ciliary artery; S= supratrochlear artery; Ss= sphenoid sinus; MPC= medial posterior ciliary artery; E= ethmoidal air cells; Mb= muscular branch of the ophthalmic artery.

According to our dissections, 75% of the posterior ethmoidal artery (26 cases) crossed over the superior oblique muscle and consequently crossed over the trochlear nerve as well (Figure 5). However, in six cases the artery was seen to run between the upper margin of the oblique superior and the trochlear nerve and thus crossed beneath the latter.

DISCUSSION

Acquired trochlear nerve palsy has been associated with head trauma, vascular disease, and neoplasm. In many cases, the causes remain unclear (15,16). Isolated trochlear nerve palsy is an uncommon occurrence. The majority of cases are caused by trauma, diabetes mellitus, or vascular disease (17,18,19). Occasionally, trochlear nerve palsy may be due to compression by a tumor in the cerebellopontine angle (20).

We found the gap between the origins of the two trochlear nerves as a mean 7 mm (range 4.6 to 9.4), but Villain et al. measured a mean 8.8 mm (range 6 to 12 mm). We measured the total length of the infratentorial part of the trochlear nerve as 32.1 mm (range 26.3 to 36.7 mm). According to Villain et al., the total length of the infratentorial part or the trochlear nerve was 34.4 mm (range 25 to 39 mm) (1).

Along the infratentorial course the trochlear nerve has a close relationship with the cerebellum, the cerebral peduncle and the tentorium cerebelli. It reaches the lower margin of the free edge of the tentorium at the posterior edge of the cerebral peduncle. We can also state that this nerve have a close relationship with the superior cerebellar artery during its course along the tentorium cerebelli, as has been previously reported in several publications (1, 21). The 23 trochlear nerves crossed the superior cerebellar artery or its collaterals one or more times. In 16 cases out of 23, the trochlear nerve was usually under the artery (%69). Villain noted that they usually found the superior cerebellar artery under the trochlear nerve (1). According to Saeki and Rhoton, the relationship of the fourth cranial nerve and the superior cerebellar arteries was found in 50 cases (22).

In our study, all of the trochlear nerves were under the plane of the incisura tentorii. Incision and retraction of the tentorium are commonly required to gain access to lesions around the incisura. The incision in the tentorium to expose the inter-peduncular and prepontine cisterns is usually located just anterior to the point where the trochlear nerve enters the free edge of tentorium. The free edge of tentorium may be retracted by means of sutures placed near it, but special care is required to avoid stretching and damaging the trochlear nerve in its course inferomedially to, and entering, the free edge of tentorium near the posterior margin of the oculomotor trigone.

According to Inoue et al., the entrance distance into the free edge of the tentorium between the trochlear nerve and the oculomotor nerve varied from 4.8-15.0 mm (average 9.4 mm), and the same distance between the trochlear nerve and the trigeminal nerve varied from 3.9-13.5 mm (average 6.6 mm) (3). In this study, we found the mean entrance distance into the free edge of tentorium between the trochlear nerve and the oculomotor nerve to be 7.9 mm (range 4.4 to 12.1 mm), and the same distance between the trochlear nerve and the trigeminal nerve was found to be 5.7 mm (range 3.1-11.7 mm).

We found the mean length of the intracavernous part of the trochlear nerve to be 24.4 mm (range 17 to 28.3 mm). In the past, Villain found the mean length of the intracavernous part of the trochlear nerve to be 26.83 mm (range 19 to 33 mm) (1).

As it enters into the orbit, the fourth nerve passes the superior orbital fissure lateral to the common annular tendon, then crosses the superomedial margin of the frontal nerve. In the region of the common annular tendon, the fourth nerve is tightly attached to the tendons; it takes a course through a tunnel of tendon tissue superomedially. The trochlear nerve's course is outside the muscle cone, and it crosses the third nerve and the optic nerve. Our findings were similar to Morard's findings on the course of the trochlear nerve in the superior orbital fissure (23). In our study, 26 trochlear nerves pass through the superior orbital fissure in a similar manner. Only in six cases, we found the trochlear nerves just superior to the frontal nerves.

According to Villain the mean length of the intraorbital part of the trochlear nerve was 25.1 mm (range 18 to 34 mm) (1). In this study, we found the mean length of the intraorbital part of the trochlear nerve to be 22.6 mm (range 16 to 31.5 mm).

The trochlear nerve has a close relationship with the posterior ethmoidal artery. The cross-section of the posterior ethmoidal artery and the trochlear nerve is 63%, according to Ducasse, (24) and 60%, according to Villain (1). In our study, this proportion was 75%.

CONCLUSION

During an operation, the identification and preservation of the trochlear nerve may be difficult because of its very thin and fragile structure. It should be emphasized that, as with any cranial and orbital surgery, the surgeon must have a working knowledge of the anatomy of the trochlear nerve and sufficient training and experience to minimize the complications.

REFERENCES

1. Villain, M., F. Segnarbieux, F. Bonnel, I. Aurby, B. Arnaud: The trochlear nerve: anatomy by microdissection. Surg. Radiol. Anat. 15: 169-173, 1993.
2. Rosenberg M.: Neuro-ophthalmology. In: RH. Wilkins, SS Rengachary (eds): Neurosurgery. 1996 Mc Graw-Hill Co. New York, page: 87-118
3. Inoue T., AL JR. Rhoton, D. Theele, ME. Barry: Surgical approaches to the cavernous sinus: A microsurgical study. Neurosurgery 26: 903-932, 1990
4. Rush JA., BR. Younge: Paralysis of cranial nerves III, IV and VI; cause and prognosis in 1000 cases. Arch. Ophthalmol. 99: 76-79, 1981.
5. Harris FS., AL JR. Rhoton: Anatomy of the cavernous sinus. J Neurosurg 45: 169- 180, 1976
6. Rhoton AL JR., DG. Hardy, SM. Chamters: Microsurgical anatomy and dissection of the sphenoid bone, cavernous sinus and sellar region, Surg Neurol 12: 63-104, 1979.
7. Lang J.: Praktische Anatomie, Begr vR von Lanz, W Wachsmuth, Fortget u hrsg V. J Lang, W. Wachsmuth, Vol I, part IB, Berlin Springer 1979.
8. Parkinson D.: Collateral circulation of the cavernous carotid artery: Anatomy. Can J Surg 7: 251-268, 1964.

9. Dolenc V.: Direct microsurgical repair of intracavernous lesions. J Neurosurg 58: 824-831, 1983.
10. Dolenc V., T. Kregar, M. Ferluga, M. Fettich, A. Morina: Treatment of tumors invading the cavernous sinus, in Dolenc VV (ed): The Cavernous Sinus. 1987 Springer-Verlag New York, page: 377-391
11. Al-Mefty O., RR. Smith: Surgery of tumors invading the cavernous sinus. Surg Neurol 30: 370- 381, 1988.
12. Krist A., D.W. Barnett, DL. Barrow, G. Bonner The Blood supply of the Intracavernous Cranial Nerves: An Anatomic Study Neurosurg 34: 275-279, 1994.
13. Sekhar LN., G. Lanzino, CN. Sen, S. Pomonis: Reconstruction of third through sixth cranial nerves during cavernous sinus surgery. J. Neurosurg. 76: 935-943, 1992.
14. Grimson BS., MJ. Ross, G. Tyson: Return of function after intracranial suture of the trochlear nerve. J. Neurosurg. 61: 191-192, 1984
15. De Benedittis G., V. Bernasconi, and G. Ettore: Tumours of the fifth cranial nerve. Acta Neurochir. 38: 37-64, 1997.
16. Ghatak NR., CW. Norwood, CH. Davis: Intracerebral schwannoma. Surg. Neurol. 3: 45-47, 1975.
17. Boggan JE. , ML. Rosenblum, CB. Wilson: Neurilemmoma of the fourth cranial nerve; Case report. J. Neurosurg. 50: 519-521, 1979.
18. Curight H., P. Hansatia: Isolated fourth cranial nerve palsies; Etiology, and prognosis. Wis. Med. J. 76: 26-28, 1977.
19. Younge BR., F. Sutula: Analysis of trochlear nerve palsies; Diagnosis, etiology, and treatment. Mayo Clin. Proc. 52: 11-18, 1977.
20. Burger LJ. , NH. Kalvin, LJ. Smith: Acquired lesions of the fourth cranial nerve. Brain 93: 567-574, 1970.
21. Kings JS.: Trochlear nerve sheath tumour; Case report. J. Neurosurg. 44: 245-247, 1976.
22. Saeki N., AL. Rhoton: Microsurgical anatomy of the upper basilar artery and the posterior circle of Willis J. Neurosurg 46: 563-578, 1977.
23. Morard M.,Tcherekayev V, Tribolet N: The Superior orbital fissure: A microanatomical Study. Neurosurgery 35: 1087-1093, 1994.
24. Ducasse A., JB. Flament, A. Segal: Etude anatomique de la vascularisation et de l'innervation des muscles obliques de l'oeil. Ophtalmologie. 5: 5-8, 1991.

INNERVATION PATTERN OF LIP AFTER NASOLABIAL FLAP OPERATION

Ali Teoman Tellioğlu* • İbrahim Tekdemir** • Müfit Akyüz***

SUMMARY

Dernervation problems of the lip both the upper lip and reconstructed lower lip have been considered possible after nasolabial flap procedures particularly in bilateral cases. We performed gate flap operations in five patients for lip defects due to squamous carcinoma excision. Lip innervation was investigated with EMG studies in the postoperative period. We observed that innervation of the lip was present in early postoperative period. After this clinical finding an anatomic study was performed on five cadavers. Ten nasolabial flaps were elevated to examine lip innervation. An area which can permit neural pathways for upper lip was localized between the most cephalic borders of the nasolabial flap and the lateral wall of the pyriform apertura then. Then necropsies were taken from this area. Ample neural tissue was identified with histologic examination. In conclusion, nasolabial "gate" flap provides ideal lower lip reconstruction with innervated tissue and upper lip innervation is protected with bilateral gate flap operation.

Key words: *Nasolabial flaps, gate flap, lip innervation*

ÖZET

Nazolabial Flep Operasyonlarından Sonra Dudağın İnnervasyon Paterni

Özellikle iki taraflı nazolabial flep operasyonlarından sonra dudağın denervasyon problemleri olabileceği düşünülmüştür. Biz sukuamoz karsinoma sonrası beş olguda ortaya çıkan defektleri nazolabial "gate" flap ile onardık. Dudak innervasyonunu postoperative dönemde EMG ile araştırdık. Erken postoperative dönemde bile dudağın innervasyonu olduğunu gözledik. Bu klinik bulgu sonrası beş kadavra üzerinde bir anatomik çalışma yaptık ve 10 nazolabial flebi dudağın innervasyonunu araştırmak için kaldırdık. Bu çalışma sırasında üst dudağa sinir iletimine izin veren nazolabial flebin en üst kenarı ile piriforum aperturanın lateral kenarı arasında bir alan lokalize edildi. Ardından bu alandan nekropsiler alındı ve çok fazla sinir dokusu histolojik incelemede gözlendi. Sonuç olarak nazolabial "gate" flap bilateral olgularda bile dudak rekonstrüksiyonun innerve dokularla yapılmasına olanak sağlayan iyi bir flep seçeneğidir.

Anahtar Kelimeler: *Nazolabial flepler, gate flap, dudak innervasyonu*

Treatment of the lower lip defects should be planned following certain principles to achieve ideal reconstruction. Reconstructed lip should have a natural appearance and an adequate buccal sulcus. Innervated tissues should be used for reconstruction and innervation of the donor site should be protected after operation. Finally, newly reconstructed lower lip must be able to permit chewing and prevent drooling with good labial consonant formation (1). Nasolabial "Gate" flap was described to fulfill all these requirements (2). It is harvested from the nasolabial sulcus and transferred to lower lip. However, total upper lip denervation with partial denervation of the reconstructed lower lip can be considered after bilateral gate "nasolabial" flap transfer because motor branches of facial nerve and sensitive branches of trigeminal nerve are sacrificed during flap elevation from the nasolabial sulcus (3).

Fortunately, we have observed that our patients in whom reconstruction was accomplished using gate flap, have not suffered from denervation of the upper lip and new reconstructed lower lip even in early postoperative period. The innervation pattern of the lip after gate flap operation was assessed with EMG studies. Furthermore, an anatomic and histologic study was performed to explain our clinical findings.

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MATERIALS AND METHOD

Five patients who had a lower lip defect after the excision of squamous cell carcinoma were reconstructed with nasolabial flaps. All operations were performed in the Ankara Oncology Hospital. Four patients were male and one patient was female. Preoperative biopsy confirmed squamous cell carcinoma of the lower lip in all patients. Defect size after tumor excision varied from 3 to 8 cm. Unilateral nasolabial flap was carried out only one case (Table 1). Design of the nasolabial gate flap was modified to avoid macrostomia in two patients. This modification was described by Seyhan and coworkers (3). EMG, an objective documentary was preferred for investigation of lip innervation. Motor function of the orbicular oris muscle was studied with EMG. The EMG studies were performed by Medelec MS-92 EMG unit. These studies were performed on proximal (Y) and distal (Z) portions of the flap and filtrum (X) of the upper lip (Fig. 1). Presence or absence of motor unit potentials were recorded. The facial nerve was stimulated beside the tragus and the response was also recorded as present or absent. Postoperative wound care was completed in 10 days after operation in all patients and EMG studies were immediately performed.

Studies were repeated at the end of the first month in 4 patients. Ten nasolabial flaps were elevated in 5 cadavers to investigate whether there was any connection permits neural pathways for upper lip innervation. After elevation of nazdabial flabs, an area was localized between the most cephalic border of the nasolabial flap and the lateral wall of the pyriform apertura, under the nasal base (Fig 2,3). Canse quentry, Necropsies were taken from this area to show neural tissue histologically. All specimens were stained with hematoxylen and eosin for light microscopy.

RESULTS

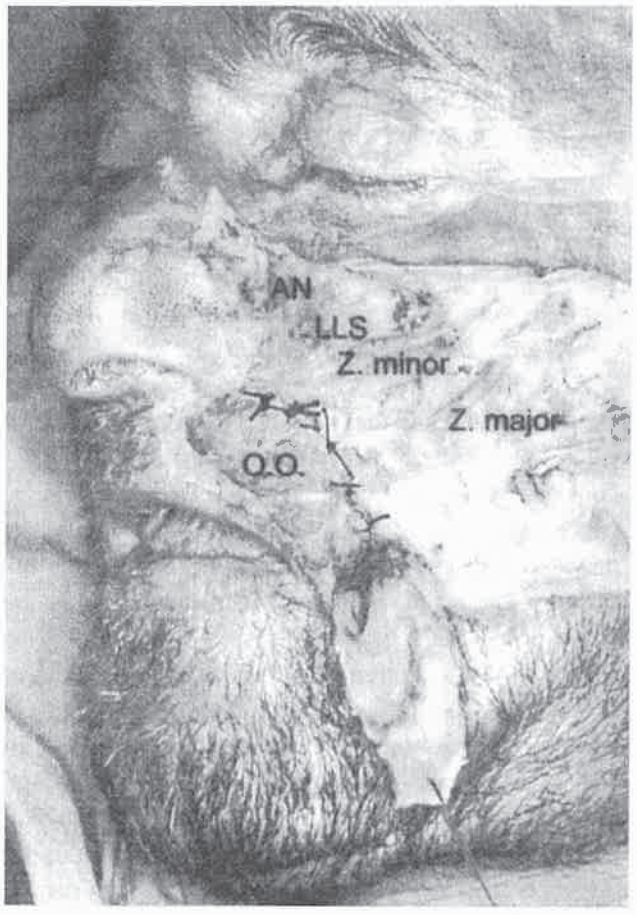
Functional and aesthetic results were satisfactory in all patients. Flap edema with generalized head edema was observed in one patient who had bilateral suprahyoid dissection. It resolved in 2 months postoperatively. Partial mucosal necrosis was observed in

Figure 1. Needle EMG studies were performed on the proximal (Y), distal (Z) parts of flap and donor site (X).

Table 1. Patients' characteristics

Case	Etiology	Defect	Operation	Complication	Follow-up (month)
56-year old Male	SCC		Bilateral gate flap	Flap edema	12
53-year old Female	SCC		Bilateral gate flap	Mucosal Necrosis	11
48-year old Male	SCC		Bilateral fate flap		9
75-year old Male	SCC		Modified unilateral gate flap		7
51-year old Male	SCC		Modified bilateral gate flap		7

SCC: Squamous Cell Carcinoma



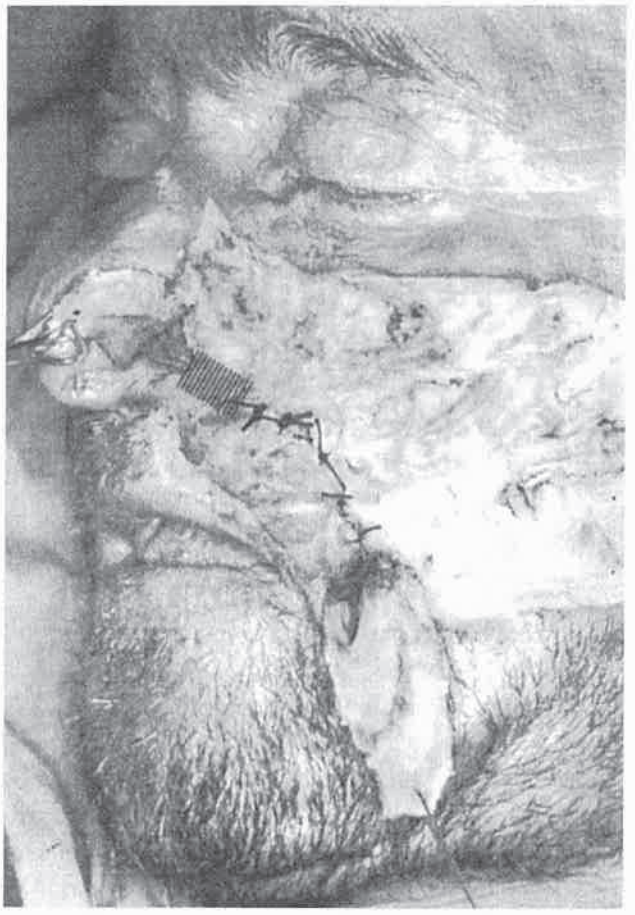


Figure 2 and 3. A nasolabial flap was harvested in cadavers. Then alar base was elevated and necropsy was taken doted area to search nerve tissue for upper lip innervation.

another patient. It was managed with local wound care. Motor innervation of both reconstructed lower lip and donor site was proven by EMG studies even in the early postoperative period. (Table 2).

In anatomical study, an area was identified between the most cephalic border of the nasolabial flap and the lateral wall of the nasal cavity under the alar base. It was considered that this area enabled some neural pathways for upper lip innervation. Necropsies which were taken from this area, were examined with light microscopy and then ample neural tissues were identified to innervate the upper lip (fig 4).

Table 2. EMG studies

	Presence of MUPs*					Response to facial nerve stimulation				
	Flap L		Flap R		Donor Site	Flap L		Flap R		Donor Site
Patients	Y	Z	Y	Z	X	Y	Z	Y	Z	X
1	+**	+	+	+	+	+	+	+	+	+
2	+	+	+	+	+	+	+	+	+	+
3	+	+	+	+	+	+	+	+	+	+
4	+	+			+	+	+			+
5	+	+	+	+	+	+	+	+	+	+

* : Motor Unit Potentials
** : MUPs are present which shows innervation
L : Left
R : Right

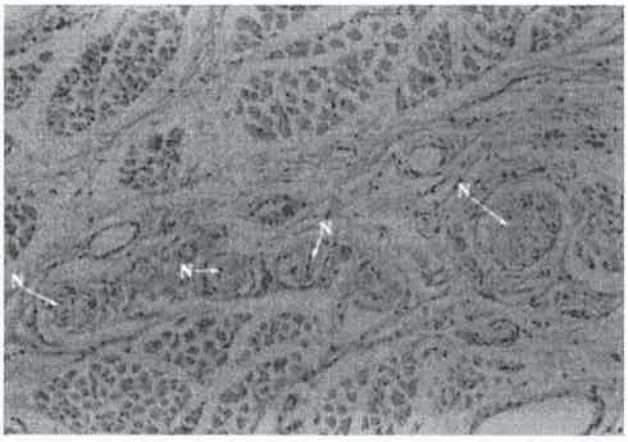


Figure 4. Histologic examination show that there are ample neural tissue for innervation of upper lip (hematoxylen and eosin, X 20).

DISCUSSION

There have been only a few reports in the literature for lower lip reconstruction with using innervated flaps. Innervated orbicular oris flap was described by Karapandzic (4). His flap provided excellent functional restoration because it preserved motor and sensoryl innervation. However, it had a drawback as microstomia which became more severe with defect size (1). Furthermore, the lower lip becomes very tight, causing a marked distortion in appearance (5).

Innervated depressor Anguli Oris flap which was described by Tobin (1) is another choice for functional lower lip repair. This technique which includes the depressor Anguli Oris muscle with overlying skin and mucosa replaces the lower lip defect and overcomes the shortcomings of the innervated orbicularis oris flap in lower lip reconstruction. However the mental nerve limits the rotation arch of this flap (6). Moreover, superiorly based Depressor Anguli Oris flap has poor lymphatic drainage resulting in flap which does not resolve for long period (7).

Recently, mental V-Y island flap was reported for lower lip reconstruction (8). The mental nerve enables sensation and the marginal mandibular nerve supplies motor innervation of this flap. It can be used to repair lower lip defects without microstomia and innervation deficit, but mental V-Y island flap cannot be applied when mental skin is sacrificed in large tumor excision or en-blok resection of a lower lip tumor with neck lympadectomy material. In addition it has unnatural appearance after reconstruction (8).

Gate flap has also been drescribed for lower lip reconstruction (2) and was modified for reconstruction of extensive lower lip defects (9). It can achieve all reconstructive goals for ideal lip repair. However, it is accepted that gate flap renders the tissue for lower lip denervated and destroys the innervation of the upper lip, because the facial and trigeminal nerve branches are cut in nasolabial sulcus which is the donor site of the nasolabial flaps. Fortunately, our clinical cases have not suffered from innervation problems. We could not find any report about innervation of reconstructed lower lip and upper lip after nasolabial flap transfer and investigatedit. EMG studies demonstrated that gate flap transferred to lower lip had innervation and that upper lip innervation was protected. This phenomena can be explained with nerve branches which enter through intact base of flap to innervate it. Furthermore, there are some neural pathways to upper lip between the most cephalic point of the nasoplabial sulcus and lateral wall of the nasal cavity for upper lip innervation. Anatomic study showed that there was sufficient space between cephalic border of flap and lateral wall of nasal cavity under alar base and histologic study proved that ample nerve tissue entered to upper lip through that space. Therefore the upper lip is protected from total denervation after nasolabial "gate" flap transfer. Nasolabial flaps can achieve ideal lip reconstruction with innervation with innervated tissues and have minimal donor site morbidity.

REFERENCES

1. Tobin G, O'Daniel: Lip reconstruction with motor and sensory innervated composite flaps. Clin Plast Surg. 1990; 7:623-632.
2. Fujimori R: Gate flap for the total reconstruction of the lower lip. Br J Plast Surg. 1992; 33:340-345.
3. Seyhan A, Gürel M, Tugsel E, Cilengir M, Alic B: Modified gate flap for lower lip reconstruction. Eur J Plast Surg . 1992; 15:86-9.
4. Karapandzic M: Reconstruction of lip defects by local arterial flaps. Br J Plast Surg.1974; 27:93-97.

5. Kroll SS: Staged sequential flap reconstruction for large lower lip defects. Plast Reconstr Surg. 1991; 88:620-625.
6. Tellioğlu AT, Akyüz M. Functional reconstruction of total lower lip defects with radial forearm free flap combined with a depressor anguli oris muscle transfer. Ann Plast Surg. 1998; 40:310-311.
7. Tellioğlu AT, Koçer U, Çelebioğlu S, Şensöz O, Akyüz M: Applications of innervated depressor anguli oris flap in lower lip reconstruction. Türk Plastik Cerrahi Dergisi.1993; 2:41-45.
8. Bayramiçli M, Numanoğlu A, Tezel E: The mental V-Y island advancement flap in functional lower lip reconstruction. Plast Reconstr Surg. 1997; 100:1682-1690.
9. Mavili E, Kayıkçoğlu A, Gürsu G: Modified use of gate flap for the reconstruction of the lower lip. Eur J Surg Oncology .1993; 19:327-331.

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EFFECT OF OSTIAL SURGERY ON MUCOCILIARY CLEARANCE: EXPERIMENTAL STUDY IN RABBITS

M. Cem Özbek* • Suat Turgut** • Ali Bilgili *** • Cafer Özdem*

SUMMARY

For the physician and the patient, the diagnosis and management of chronic sinonasal disease is frustrating and challenging. The keystone of functional endoscopic sinus surgery is the ability to accurately diagnose even relatively minor changes in the ostiomeatal complex that interfere with mucociliary clearance. However, surgical widening of a sinus ostium is not condemned in all cases because the integrity of the ostium is important for the normal functioning of the sinus. A study therefore was designed to evaluate if there is any way for a surgeon to be functional during ostioplasty. Widening of the natural ostium was performed anteroinferorly in the first group (n=10) and posteriorly in the second group (n=12). Eleven sinuses were used as controls. After 6 weeks all the sinuses were reexplored and mucociliary clearance was studied. Enlarging natural ostium posteriorly towards posterior fontanelle had considerable reverse effects on the overall rate of mucociliary clearance with areas of ink retention around the ostium. It therefore would appear preferable not to perform widening of the ostium posteriorly. If it is necessary to enlarge the ostium it should be done towards the less destructive anteroinferior part.

Key Words: *Antrostomy, mucociliary clearance, maxillary sinus ostioplasty, posterior fontanelle*

ÖZET

Mukosilier Aktivitede Ostial Cerrahinin Etkileri: Tavşanlar Üzerinde Deneysel Çalışma

Kronik sinüzitin teşhisi ve tadevisi hem doktor, hem de hasta için hayal kırıklığı yaratan tartışmalı bir konudur. Fonksiyonel sinüs cerrahisinin temel amacı osteomeatal kompleks bölgesinde mukosilier akımı bozabilecek en küçük değişikliklerin bile doğru olarak tanısını koymaktır. Sinüsün işlevini devam ettirebilmesi için sinüs doğal ostiumunun yapısının korunması önemli olduğundan dolayı her olguda sinüs ostiumunun genişletilmesine yönelik cerrahi girişim önerilmemektedir. Bu çalışma, osteoplasti sırasında cerrahın daha fonksiyonel bir ameliyat şansı bulunup bulunmadığını araştırmak amacıyla yapıldı. Birinci grupta (n=10) sinüs doğal ostiumu anterioinferiora, ikinci grupta (n=12) ise posteriora doğru genişletildi. Kontrol grubu olarak 11 sinüs kullanıldı. Altı hafta sonra bütün sinüsler tekrar değerlendirildi ve mukosilier akım hızına bakıldı. Doğal ostiumu posterior fontanelin bulunduğu posteriora doğru genişletilen olgularda ostium çevresinde ileri derecede mürekkep birikmesine neden olacak kadar olumsuz değişiklikler gözlendi. Doğal ostiumun posteriora genişletilmesinin tercih edilmemesinin daha uygunu olacağı düşünüldü. Sinüs ostiumu eğer genişletilmek isteniyorsa bu işlemin daha az destrüktif olan anteroinferior bölüme doğru yapılması gerektiği sonucuna varıldı.

Anahtar Kelimeler: *Antrostomi, mukosilier aktivite, maksiller sinüs osteoplastisi, posterior fontanel*

In the early part of this century, before the introduction of modern methods, windows between the maxillary sinus and nasal cavity were created in the middle meatus or in the inferior meatus (1,2,3,4,5). However in the following years, it was found that all mucociliary transport occurs through the natural ostium rather than through nasoantral windows.[6] Thus, enlargement of the natural ostium gained popularity. Messerklinger introduced the concept of functional endoscopic sinus surgery (7). The principle of the technique is limited resection of inflammatory or anatomic defects that interfere with normal mucociliary clearance and result in localized persistent inflammation (6,8).

The main two purposes of the functional endoscopic sinus surgery (FESS) are the ventilation of paranasal sinuses as well as normalizing the mucociliary transport (9,10).

By enlarging the natural ostium ventilation of the maxillary sinus is provided but mucociliary clearance-important in sinus physiopathology-is frequently neglected.

As the FESS gained popularity surgeons started to impact on the lateral nasal wall, with the destruction

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of the tissue whether it is diseased or not, the FESS became a destructive surgical procedure instead of being functional.

As a result of these destructive inclinations, the natural structure of the natural ostium has also been destroyed. In 1989 Kennedy and Shaalan (11) published a study investigating mucociliary clearance using "non-pasteurella-free rabbits" and concluded not to perform widening of the ostium in patients unless the ostium is closed or stenotic. But in some situations it is necessary to perform ostioplasty as in the cases of stenosis or massive edema. This study was performed to evaluate if there is any way for a surgeon to be functional during ostioplasty and the effects of enlargement of the maxillary sinus ostium whether anteroinferiorly or posteriorly to the sinus mucociliary clearance.

MATERIALS AND METHODS

Seventeen New Zealand white rabbits without signs of upper respiratory tract infection (no nasal discharge) are included in the study. All rabbits underwent induction of anesthesia with an intramuscular injection of 50mg/kg ketamine hydrochloride and 2mg/kg diazepam. Ketamine hydrochloride was reinjected at 45 minute intervals if it was necessary. The area of the nasal dorsum was shaved, disinfected and draped. A paramedian incision was made through the skin, subcutaneous tissue and periosteum. The periosteum was elevated and the bone of the superior wall of the sinus was removed with a drill. A plastic drape was applied to prevent external air from entering the sinus and a small perforation was made for endoscopic inspection. The sinus mucosa was irrigated frequently with saline to prevent drying and disturbance of mucociliary transport. A few drops of indian ink were introduced into the sinus to observe mucociliary transport.

The animals were divided into 3 groups. Experimental controls were created by only exposing the maxillary sinus on one side in 11 sinuses. In 12 sinuses the natural ostium of the sinus was widened posteriorly towards posterior fontanelle (including posterior fontanelle). In the other 10 sinuses the natural ostium of the sinus was widened anteriorly and inferiorly. One of the 34 sinuses was excluded from the study because of difficulty during operation. After these procedures the incision was closed with 3-0 nylon sutures. The animals were treated prophylactically with antibiotics for 10 days.

After 6 weeks, all the sinuses were reexplored and examined in the same manner as on the day of surgery. The appearance of mucosa and presence or absence of discharge was observed. The mucociliary transport was studied and documented with serial photographs. After all the procedures had been completed the animals were killed painlessly with an intravenous injection of an overdose of pentobarbital sodium.

RESULTS

At the initial operation, all of the sinuses appeared free of infection (Fig. 1). Mucociliary clearance was normal in all animals and was noted to be similar to that previously reported in humans and rabbits, spreading out in a star-shaped pattern from the floor, up the walls and acceleration of transport towards the ostium (Fig. 2).11,12 Mucociliary transport was markedly slowed or stopped as a consequence of prolonged exposure to air flow and dryness. The ink moved at a speed of 7 to 10 mm/min.

Control Group (n=11): In the control group, only one sinus (9%) had evidence of infection. Mucociliary transport was delayed in the infected sinus and normal in all other sinuses. The ink was seen to pass through the ostium towards nasal cavity in all of the sinuses.

Ostioplasty Group (n=22): The ostioplasty group was divided into two according to the widening place of the natural ostium. In the first group (n=12) all the maxillary sinus ostia were widened posteriorly towards posterior fontanelle. In the second (n=10) group enlarging was done anteriorly and inferiorly.

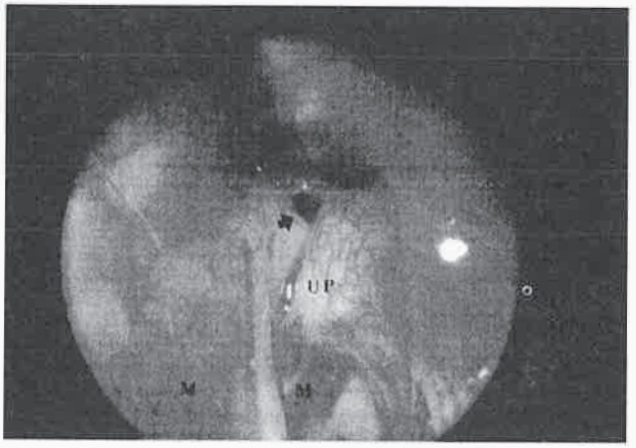

Figure 1: Integrity of the maxillary sinus before operation. UP: Uncinate process, Arrow: Maxillary sinus natural ostium, M: Mucosa of the sinus.

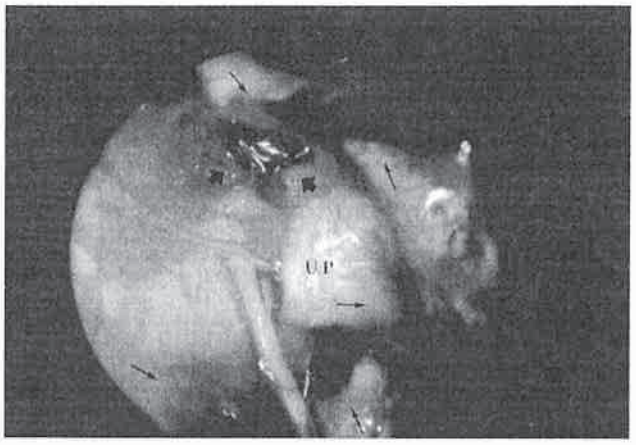

Figure 2: The ink is spreading out in a star-shaped pattern from the floor up the walls towards ostium. UP: Uncinate process, Thick Arrow: Maxillary sinus natural ostium, Thin Arrow: Ink spreading out towards ostium.

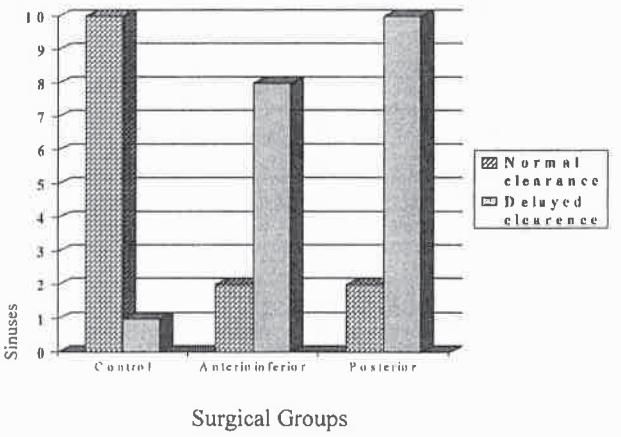

Figure 3: Incidence of infection seen in different operative groups.

In the ostioplasty group (n=22) infection was present in 10 sinuses (45.4%). Although mucociliary clearance was present in all of the sinuses it was normal in only 4 (18.1%) of them. Mucociliary transport was markedly slowed in the remaining 18 (81.8%) sinuses.

In 6 (33.3%) of the 18 sinuses in which mucociliary transport was slowed, the ink was seen to leave the sinus through the natural ostium but in the remaining 12 sinuses the dye tended to collect arround ostium instead of passing to the nasal cavity.

The ink was seen to pass through the ostium in the 4 sinuses in which mucociliary clearance was normal.

In the sinuses with an enlarged ostium towards posterior fontanelle, 6 had evidence of infection and in 8 (66.6%), the ink failed to pass through ostium.

In the second group with widened ostium anteriorly and inferiorly, in 4 sinuses (40.0%) the dye did not exit to the nasal cavity and all of these sinuses were infected.

Comparison between groups: The results show that, infection occurred in only 1 (9.1%) of the 11 sinuses in the control group whereas infection occurred in 10 (45.4%) of the sinuses in which the natural ostium was surgically enlarged (Fig. 3).

Mucociliary transport was delayed in 18 (81.8%) sinuses in the ostioplasty group but was slow in only 1 (9.1%) in the control group (Fig. 4). Passage through natural ostium was present in all sinuses in the control group whereas it was absent in 10 (45.4%) in the surgical group (Fig. 5). Mucociliary clearance rate and passage of the ink through the ostium between the control and surgical groups was statistically significant ($p<0.05$ x^2 test). The difference in the rate of infections between the 2 groups is not statistically significant($p>0.05$ x^2 test). However the rate of infection was 45.4% in the ostioplasty group and 9.1% in the non surgical group.

After than, the results were compared between the two surgical groups. There were no statistical differences in the rate of infection, mucociliary clearance rate and passage through the ostium between the surgical groups in which the natural ostium was enlarged posteriorly or anteriorly and inferiorly.

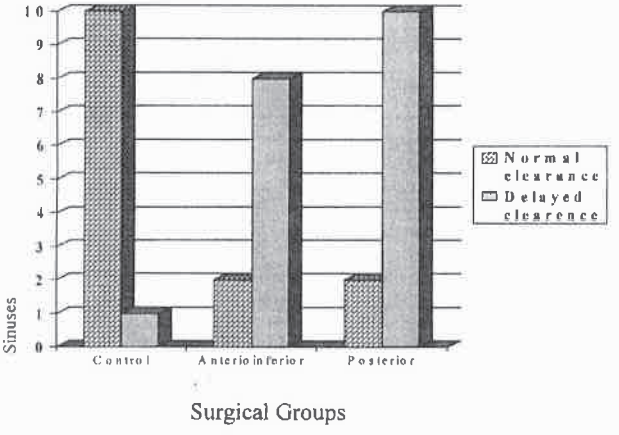

Figure 4: Frequency with which mucociliory celarance was present in different operative groups.

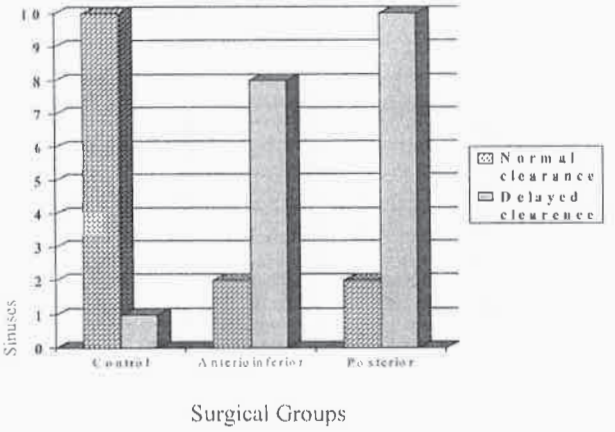

Figure 5: Frequency of passage through ostium seen in different operative groups.

However passage through the ostium was present in the 4 (33.3%) sinuses in which the ostium was enlarged posteriorly, whereas passage occured in 6 (60.0%) sinuses in which the ostium was enlarged anteroinferiorly.

Although statistically no difference was found, dye tended to collect inferiorly in the area in which the ostium had been extended posteriorly.

DISCUSSION

The advantages of the functional endoscopic technique include improved diagnostic accuracy and visualization during surgery, and the ability to minimize trauma to normal structures.

Messerklinger (6) introduced the concept of functional endoscopic sinus surgery based on his careful endoscopic observation and his studies of sinus mucociliary clearance in both healthy and diseased mucosa. The principle of the technique is limited resection of inflammatory or anatomic defects that interfere with normal mucociliary clearance and result in localized persistent inflammation. However, it became popular to enlarge maxillary sinus natural ostium whether it is diseased or not. Thus enlargement of the ostium is believed by many to be the ideal treatment for chronic sinusitis (7,13). Some investigators believe that surgical trauma to the maxillary ostium should be avoided since this structure has an important role in the function of the maxillary sinus. In 1940, Zange (14) concluded from his histological study in humans that the maxillary ostium could not be damaged without negative consequences. Hilding (15) demonstrated, in rabbits, that enlargement of the maxillary ostium resulted in infections of the sinus.

Kennedy (8) in 1985 stated that, the natural ostium of the maxillary sinus should be opened in the presence of stenosis, so as to provide normal mucociliary drainage.

In the literature Hilding (16) was the first who performed a number of experiments on animals by stripping mucosa from the frontal sinuses. He reported difficulty identifying mucociliary clearance in the rabbit and attributed this to the anesthesia. By the help of intermittent irrigation and the application of an adhesive plastic drape it was possible to observe mucociliary clearance for hours so the problem of Hilding appears to be due to drying of the mucosa from the open sinus. As in the maxillary sinus of humans, mucociliary clearance was seen to spread out in a starshaped pattern from the floor and then pass up the walls to the ostium. In 1989, Kennedy and Shaalan (11) published a study investigating mucociliary clearance using "non-pasteurella-free" rabbits. They found a considerable reduction in the rate of mucociliary clearance in the area of the widened maxillary sinus ostium concluded not to perform widening of the natural ostium unless the ostium is closed or stenotic.

In a study primarly designed to evaluate the effect of enlargement of the maxillary sinus ostium and the effect of a nasoantral window away from the ostium on sinus infection rates, Perko and Karin found that widening of the ostium interfered with mucociliary transport through the ostium and induced infections (12). The results of the present study also indicate that enlarging the natural ostium induce infection as the infection rate was 9.1% in the control group whereas it was 45.4% in the ostioplasty group. However, in the ostioplasty group the infection rate was 45.4% but the mucociliary clearance rate was weaker in 81.8% of the sinuses. Based upon these observations it is obvious that additional factors must be necessary to explain the difference. Another finding is that, interference with mucociliary transport through the ostium in the posteriorly widened group is higher (66.7%) than the anteroinferiorly widened group (40.0%). Altough the difference between the two groups is not significant statistically, in the posteriorly widened group the mucociliary clearance had a tendency to be weaker.

The ink was seen to pass through the ostium in 10 (45.4%) of the 11 sinuses in the ostioplasty group. This finding seems to be low when compared with the study of Kennedy and Shaalan as the passage of ink through the ostium occured in 61% of the sinuses. However the dye passed through the ostium in 4 sinuses (33.3%) in the posteriorly widened group and in 6 (60.0%) in the anteroinferiorly widened group. The results of the study were similar with the results of anteriorly and inferiorly enlarged group in our study.

The findings of the present study indicate that enlarging natural ostium posteriorly towards posterior fontanelle had considerable reverse effects on the overall rate of mucociliary clearance with areas of ink retention around ostium. In the literature there is no other study discussing the effect of posterior fontanelle on mucociliary clearance rate. Posterior fontanelle is a membranous wall just posterior to the maxillary sinus ostium and inferior to the lamina papyracea. The fontanelle may be divided into anterior and posterior segments by the uncinate process. The posterior fontanelle lies above the posterosuperior edge of the uncinate process.

As a result of these findings it therefore would appear to argue against routine widening of natural ostium of the maxillary sinus and caution should be used when dealing with the maxillary sinus ostium. It would be preferable not to enlarge natural ostium routinly as the principle of the procedure is to be functional not destructive and widening natural ostium has absolutely negative effects on sinus physiology. However if it would be necessary to enlarge the ostium, it should be done towards the less destructive anteroinferior part, not posteriorly towards posterior fontanelle.

REFERENCES

1. Lavelle RJ, Spencer HM. Infection of the Maxillary Sinus: The Case For Middle Meatal Antrostomy. Laryngoscope 1971; 81:90-106.
2. Legler U. Surgical Drainage of the Maxillary Sinus Through the Inferior Meatus. Rhinology 1981; 19:25-9.
3. Straatman NJA. and Buiter T. Endoscopic Surgery of the Nasal Fontanel. Arch Otolaryngol 1981; 107:290-3.
4. Buiter CT. Nasal Antrostomy. Rhinology 1988; 26:5-16.
5. Huizing EH. Functional Surgery in Inflammation of the Nose and Paranasal Sinuses. Rhinology 1988; (Suppl 5):5-15,.
6. Messerklinger W. Endoscopy of the Nose. Baltimore, Urban & Schwarzenberg, 1978.
7. Messerklinger W. Das Infundibulum Ethmoidale und Seine Entzündlichen Erkrankungen. Arch Otolaryngol 1979; 222:11-22.
8. Kennedy DW. Functional Endoscopic Sinus Surgery: Technique. Arch Otolarygol 1985; 111:643-9.
9. Stammberger H, Posawetz W. Functional Endoscopic Sinus Surgery:Concept, Indications and Results of the Messerklinger Technique. Eur Arch Otorhinolaryngol 1990; 247:63-76.
10. Dal T, Onerci M, Cağlar M. Mucociliary Function of the Maxillary Sinuses After Restoring Ventilation: A Radioisotopic study of the Maxillary Sinus.
11. Kennedy DW, Shaalan H. Reevaluation of Maxillary Sinus Surgery:Experimental Study in Rabbits. Ann Otol Rhinol Laryngol 1989; 98:901-6.
12. Perko D, Karin RR. Nasoantral Windows: An Experimental Study in Rabbits. Laryngoscope 1992; 102:320-6.
13. Stammberger H. Endoscopic Endonasal Surgery-Concepts in Treatment of Recurring Rhinosinusitis. Part II. Sugical Technique. Otolaryngol Head Neck Surg 1986; 94:147-56.
14. Zange J. Das Schwellgewebe der Nase besonders in seiner Beziehung zu den Nebenhöhlen and ihren Ausführgangen. Arch Ohr-Nas-Kehlkpf Heilk 1940; 147:103-13.
15. Hilding AC. Experimental Sinus Surgery:Effects of Operative Windows on Normal Sinuses. Ann Otol Rhinol Laryngol 1941; 50:379-92.
16. Hilding AC. Experimental Surgery of the Nose and Sinuses. Results Following Partial and Complete Removal of the Lining Mucosa Membrane From the Frontal Sinus in the Dog. Arch Otolaryngol 1933; 17:760-8.

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ENDOCRINE PROFILE IN MEN WITH VARICOCELE

Talat Yurdakul

SUMMARY

Although varicocele has long been known to cause testicular dysfunction, the pathogenesis of such a dysfunction remains uncertain. Varicocele clinically manifest at the time of puberty. Changes in testicular volume and consistency in the ipsilateral testis have been reported as being more significant in high-grade situations. Controversy continues about the effects of varicocele on the hormonal function of the testis. There is also no agreement on the beneficial effects of varicocele repair on hormonal dysfunction.

It was therefore considered worthwhile to investigate this problem further, especially in regard to endocrine alterations and the effects in both the pathogenesis and the therapeutic outcome of varicocele.

Key Words: *Varicocele, Hormones, Leydig Cell, and Surgery*

ÖZET

Derleme: Varikoselde Hormonal Profil

Varikoselin testis fonksiyonunu bozduğu uzun zamandır bilinmesine rağmen bunun patogenezi tam olarak ortaya konulamamıştır. Varikosel pubertede klinik olarak belirgin hale gelerek özellikle yüksek grade'li olgularda testis hacminde ve kıvamında değişikliklere yol açar. Varikoselin testisin hormonal işlevlerine etkisi ile ilgili tartışmalar halen sürmektedir. Varikosel onarımının hormonal disfonksiyonu düzelttiği konusunda da bir fikir birliği yoktur.

Biz endokrin değişikliklerin varikoselin patogenezine olan katkısını ve tedavinin gidişine olan etkisini incelemeğe değer bulduk.

Anahtar Sözcükler: *Varikosel, Hormonlar,Leydig Hücresi, Cerrahi*

HORMONE LEVELS AND GONADOTROPINE STIMULATION TESTS

It is well known that 10 to 30 per cent of male sub fertility can be attributed to testicular dysfunction caused by varicocele. The exact path physiology of varicocele is incompletely understood. Despite the decreased or normal testosterone (T) levels reported in numerous studies, controversy has continued concerning the effects of varicocele on the hormonal functions of the testis. What is known is that spermatogenesis and sperm maturation take place in different parts of the male reproductive tract, and both processes depend, among other factors, for the hormonal concentration prevailing in each particular part.

Adamopoulus et al. measured FSH, LH, PRL, T, E1, E2 and sex hormone binding globulin (SHBG) concentrations simultaneously in the accessible compartments of the male genital tract in normospermic men and oligospermic patients with varicocele and defined important aspects of the endocrine milieu prevailing in the male reproductive tract. They demonstrated a change of the relative activity of androgens and estrogens from the testis to the seminal fluid (1). A number of studies have indicated normal circulating and spermatic cord serum hormone levels in patients with varicocele (2,3), and decreased bilateral intratesticular testosterone levels in experimentally induced left varicocele (4). In 1981, Nagao et al. measured hormonal and seminal parameters in fertile and infertile men with varicocele. Both groups were shown to have abnormalities that were more pronounced in the infertile group, suggesting an underlying process in varicocele that eventually leads to infertility (5).

Of particular note is the 1989 study by Castro-Magana showing the normal histology in testicular biopsies of adolescents, but Leydig cell dysfunction, as evidenced by an abnormal serum response to the gonadotropin-releasing hormone and human chorionic go-

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nadotropin administration (6). Studies demonstrating decreased testicular responsiveness to an injection of human chorionic gonadotropin suggest a dysfunction at the Leydig cell level (7). Other studies of men with varicocele showed an exaggerated LH and FSH response to GnRH (8). Regarding these observations, Su et al. supported the hypothesis that the presence of a varicocele might induce testicular hormonal dysfunction (9). The exaggerated FSH response is due to spermatogenetic damage and decreases the secretion of the tubular factor, such as inhibin secreted from Sertoli cells, which inhibits FSH secretion (10). The increase of the LH response to GnRH in men with varicocele may well be a consequence of damage to spermatogenesis but could also be provoked by Leydig cell dysfunction.

Leydig cell hyperplasia in association with varicocele was reported by Dubin and Hotchkiss (11). However, Weiss et al. evaluated Leydig cell density quantitatively in bilateral testicular biopsies from a group of oligospermic men with varicocele (12). The Leydig cell number in their group of patients was apparently not increased, but possibly somewhat decreased. In another study, the same authors determined the testosterone levels from the testicular tissue of 16 men with a clinical varicocele by using an in vitro technique of an incubation of the testicular tissue with radiolabel androgen precursors, and found sperm counts of less than 10 million/ml (13). Although circulating T and LH levels were within normal range, a significant suppression of in vitro testosterone formation was observed in almost 90 per cent of the patients. In addition, an increased Leydig cell number was observed in testes with the highest in vitro testosterone formation. They concluded that these findings were suggestive of a disturbance of Leydig cell function. Since in all patients' plasma testosterone levels were within the normal range, this disturbance would not have been detected in individual patients on the basis of these levels alone. However, when the patients were grouped according to the in vitro testosterone synthesis data, a correlation with circulating testosterone levels was noted. The possibility of Leydig cell dysfunction in men with varicocele has been suggested by other investigators (14).

To gain an understanding as to why some men with varicocele have excessive gonadotropin responses to GnRH, despite having normal circulating levels of total T and E2, Hudson conducted a retrospective study (15). The data obtained demonstrated that these men had lower than normal free T and higher than normal free E2 levels. Men with varicocele who had normal gonadotropin responses to GnRH had normal free sex steroid values. In conclusion, the altered free sex steroid levels appeared to be the result of a subtle, intrinsic defect in the testes of some men with varicocele, coupled with subsequent alterations in SHBG levels. Hudson explained this, at least in part, by the higher than normal free E2: free T ratio and by the increase in SHBG levels, which have an affinity for E2, less than that for T, and with a further reduction in free T levels, secondary to reduced testicular androgen production, in some men with varicocele. The excessive gonadotropin responses to GnRH indicated a reduction in the negative feedback, by the testes, on the hypothalamic-pituitary axis. Other evidence for decreased androgen levels and action in men with varicocele has been provided. Hudson et al. found lower than normal seminal plasma DHT levels in the absence of genital tract obstruction, indicating a decreased 5a -reductase activities in the epididymis, which is likely a result of decreased androgen action (16).

To explain the factors affecting the quality of semen in this condition several studies have been conducted. The thickening of intratesticular blood vessels and the alteration in the metabolism of the testicle, as well as the stasis of the blood circulation in the latter, were proposed as the causes of hypoxia and the degeneration of tissues in it, which in turn the production of testicular hormones that harm spermatogenesis (17,18). Hampl et al. compared the hormonal steroid levels of oligo and oligoasthenospermic men with palpable varicocele with a group of normospermic men (19). In the oligospermic group, they found insignificantly lower levels of total testosterone, significantly lower levels of dihydrotestosterone, in addition to slightly decreased LH, but increased FSH. These results imply that there are different levels responsible for the impaired androgen synthesis.

Another noteworthy study is reported by Hadziselimovic et al. They show, for the first time, that capillary endothelial pathological conditions occur before tubular testicular changes, and that endothelial thickness increases significantly with an increase in the testicular pathological condition (20). Proliferate endothelial lesions in patients with varicocele proceed tes-

ticular changes. Their results indicate that a worsening of the testicular histology was related to the duration of the varicocele.

However, the available evidence fails to establish any one factor as being dominant factor in leading to hormonal changes. In addition, there is a marked variation in the reported rates of improvement in seminal parameters, and in pregnancies, after varicocele repair. The precise reason(s) for these variations in improvement is not known. Contrary to the previous studies, McCowen et al. reported testicular testosterone values at least twice those found by other researchers (21). They speculated that this significant difference is due to the effect of varicocele related changes in local testicular steroidogenesis, and that the local testicular control relationship or mechanisms exist, apart from known gonadotropin feedback, which might explain this observation.

Although experimental left varicocele causes a bilateral increase in testicular total organ blood flow (22), the physiological ramifications of this increase in flow are incompletely understood. According to Turner et al., left varicocele does not alter vascular permeability, and so an alteration in vascular permeability is not a factor in the pathobiology of varicocele (23).

There is no exact explanation why some oligo-asthenospermic men with varicocele do not have abnormal hormonal parameters. They do not have a significant improvement in their seminal parameters even after surgery. Varicocele may not ,then, be the cause of the oligo-asthenospermia. HCG and GnRH stimulation tests can be used to predict the outcome of a surgical repair of varicocele in infertile patients. Ando et al. reported an increase in the ratio of 17-dihydroprogesterone to testosterone levels after an HCG injection. This can be explained by an enzymatic defect in the last step of testosterone synthesis in patients with varicocele (24). Scholler et al. showed decreased testosterone and excessive 17 alfa hydroxiprogesterone responses to HCG stimulation, which may point to a C17-lyase defect in the testes of a group of men who had varicoceles (25). Kazama found a significantly lower testosterone production of Leydig cells after incubation with HCG in rats, four weeks after the formation of experimental left varicocele (26).

All these studies indicate that varicocele may have detrimental effects on Leydig cells as well as on tubule seminiferi when they are under the control of FSH and when they have androgen receptors. The completion of meiosis, spermatogenesis, and the maturation of spermatozoa in the epidydimes are under androgenic control. For the first step of spermatogenesis, androgen is mandatory. For this reason, compromised Leydig cell function results in insufficient intratesticular testosterone levels and may cause the arrest of spermatozoa in the phase of primer spermatocyte or spermatid.

EFFECTS OF SURGICAL REPAIR ON HORMONAL PARAMETERS

There is no agreement on the beneficial effects of varicocele repair on hormonal dysfunction. Numerous studies can be found in the literature, however, that show an improvement in the hormonal dysfunction.

Although there were no statistical differences, Hudson et al. reported an increase in testosterone levels after 6-12 months following the surgical repair of the varicocele (27). Segenrich reported similar results in 24 patients (28). Decreased testosterone levels returned to normal after varicocele repair in patients with varicocele who had erectile dysfunction and lower than normal testosterone levels (29). Liming-Su found a significant increase in the testosterone levels after varicocele repair (9).

Hudson compared the results of free testosterone, E2, and the sex hormone binding globulin (SHBG) in patients with varicocele, who had excessive LH responses to GnRH stimulation with normal LH responses (15). The first group showed improvement in semen parameters, sex steroids, and SHBG values after surgery. No improvement in semen parameters and no pregnancy occurred in patients who had normal LH responses to GnRH stimulation.

Sofikitis and Miyogama showed the effectiveness of surgical repair of varicocele (31). They created experimental left varicoceles in 16 rabbits. Varicoceles were repaired in 8 cases. The other 8 cases did not receive any treatment. 5 months after the initial operation, the untreated group had significantly lower sperm concentrations and decreased bilateral androgen testicular androgen binding protein activities and testicular vein testosterone levels. Other studies showed an improvement in the excessive LH response to GnRH stimulation after the correction of varicocele (3,14,19).

There is no single parameter to predict which patient will benefit from varicocele repair. The hormone profile and GnRH stimulation test, however, are promising preoperative parameters for the surgical outcome.

REFERENCES

1. Adamopoulus D, Lawrence DM, Vassilopoulos P, Kapolla N, Kontogeorgos, McGarrigle: Hormone levels in the reproductive system of normospermic men and patients with oligospermia. J Clin Endocrinol Metab 1984, 59: 447-452,
2. Swerdloff RS, Walsh PC: Pituitary and gonadal hormones in patients with varicocele. Fertil Steril 1975, 26: 1006-1012
3. Rege n, Phadke A, Bhatt J, Khatri N, Sheth A, Joshi U, Vaidya R: Serum gonadotropins and testosterone in patients with varicocele. Fertil Steril 1979, 31: 413-416
4. Rafjer J, Turner TT, Rivera F, Howards SS, and Sikka CC: Inhibition of testicular testosterone biosynthesis following experimental varicoceles in rats. Biology of reproduction 1989, 36(4): 933-37
5. Nagao RR, Plymate SR, Berger RE, Perin EB, Paulsen CA: Comparison of gonadal function between fertile and infertile men with varicoceles. Fertil Steril 1986, 46: 930-935
6. Castro-Magana M, Angulo M, Canas J, Uy J: Improvement of Leydig cell function in male adolescents after varicocelectomy. J Pediatr 1989, 115: 809-813
7. Castro-Magana M, Angulo m, Canas A, Uy J: Leydig cell function in adolescent boys with varicoceles. Arch Androl 1990, 24: 73-78
8. Bickel A, Dickstein G: Factors predicting the outcome of varicocele repair for sub fertility: the value of luteinizing hormone-releasing hormone test. J Urol 1989, 142: 1230-1233
9. Su L, Goldstein M, Schlegel PN: The effect of varicocelectomy on serum testosterone levels in infertile men with varicoceles. J Urol 1995, 154: 1752-1755,
10. Fujisawa M, Hayashi A, Imanishi O, Tanaka H, Okada H, Matsumoto O, Kamidono S: The significance of gonadotropin-releasing hormone test for predicting fertility after varicocelectomy. Fertil Steril 1994, 61: 779-782
11. Dubin L, Hotchkiss RS: Testis biopsy in sub fertile men with varicocele. Fertil Steril 1969, 20: 50-54
12. Weiss DB, Rodriguez-Rigau L, Smith KD, Chowdhury A, Steinberger E: Quantification of Leydig cells in testicular biopsies of oligospermic men with varicocele. Fertil Steril 1978, 30: 305-312
13. Weiss DB, Rodriguez-Rigau L, Smith KD, Steinberger E: Leydig cell function in oligospermic men with varicocele. J Urol 1978,120: 427-430
14. Sirvent JJ, Bernat R, Navarro MA, Rodriguez TJ, Guspi R, Bosch R: Leydig cell in idiopathic varicocele. Eur Urol 1990, 17: 257-261
15. Hudson RW: Free sex steroid and sex hormone-binding globulin levels in oligozoospermic men with varicoceles. Fertil Steril 1996, 66: 299-304
16. Hudson RW, Hayes KA, Crawford VA, McKay DE: Seminal plasma testosterone and dihydrotestosterone levels in men with varicoceles. Int J Androl 1983, 6: 135-141
17. Sharpe RM: Paracrine control of the testis. Clin Endocrinol Metab 1986, 15: 199-203
18. Hudson RW: The endocrinology of varicoceles. Fertil Steril 1988, 49: 199-202
19. Hample R, Lachman M, Novak Z, Sulcova J, Starka L: Serum levels of steroid hormones in men with varicocele and oligospermia as compared to normozoospermic men. Experimental Clinical Endocrinol 1992, 100: 117-119
20. Hadziselimovic F, Herzog B, Liebundgut B, Jenny P, Buser M: Testicular and vascular changes in children and adults with varicocele. J Urol 1989, 142: 583-585
21. McCowen KD, Smith ML, Modarelli RO, Fariss BL, Reed JW: Tissue testosterone and dihydrotestosterone from bilateral testis biopsies in males with varicocele. Fertil Steril 1979, 32: 439-442
22. Turner TT, Lopez TJ: Effects of experimental varicocele require neither adrenal contribution nor venous reflux. J Urol 1989, 142: 1372-1376
23. Turner TT, Caplis LA, Rhoades CP: Testicular vascular permeability: effects of experimental lesions associated with impaired testis function. J Urol 1996, 155: 1078-1082
24. Ando S, Giacchetto C, Colpi G, Panno ML, Beraldi E, Lombardi A, Sposato G: Plasma levels of 17-OH progesterone and testosterone in patients with varicocele. Acta Endocrinol 1983, 102: 463-469
25. Scholler R, Nahoul K, Castanier M, Rotman J, Salat Baroux J: Testicular secretion of conjugated and nonconjugated steroids in normal adults and in patients with varicocele: baseline levels and time course response to HCG administration. J Steroid Biochem 1984, 20: 203-215
26. Kazama T: Effect of experimental left varicocele on rat Leydig cell function. Japan J Urol 1995, 86: 308-315
27. Hudson RW, Perez-Marrero RA, Crawford VA, McKay DE: Hormonal parameters of men with varicoceles before and after varicocelectomy. Fertil Steril 1985, 43: 905-910
28. Segenrich E, Shmuely H, Singer R, Servadio C: Andrological parameters in patients with varicocele and fertility disorders treated by high ligation the left spermatic vein. Int J Fertil 1986, 31: 200-203
29. Conhaire F, VermeulenA: Plasma testosterone in patients with varicocele and sexual inadequacy. J Clin Endocrin Metab, 40: J Clin Endocrin Metab 1975, 40: 824-827
30. Sofikitis N, Miyagawa I: effects of surgical repair of experimental left varicocele on testicular temperature, spermatogenesis, sperm maturation, endocrine function, and fertility in rabbits. Archives Andrology 1992, 29: 163-175

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PENILE FRACTURE: ULTRASONOGRAPHY AND MAGNETIC RESONANCE IMAGING FINDINGS

Cemil Yağcı* • Suat Aytaç* • İlhan Erden* • Sadettin Küpeli** • Çetin Atasoy*

SUMMARY

A penile fracture associated with a subcutaneous hematoma was found in a 41-year- old patient. Ultrasonography and magnetic resonance image findings are discussed and a brief review of the literature is presented.

Key Words: *Penis, wounds and injuries, ultrasonography, magnetic resonance imaging*

ÖZET

Penil Fraktür: Ultrasonografi ve Manyetik Rezonans Görüntüleme Bulguları

Kirkbir yaşındaki hastada subkutan hematom ile birlikte penil fraktür saptandı. Konuyla ilgili kaynaklar gözden geçirildi, ultrasonografi ve manyetik rezonans görüntüleme bulguları tartışıldı.

Anahtar Kelimeler: *Penis, travma ve yaralanmalar, ultrasonografi, manyetik rezonans görüntüleme*

Traumatic rupture of the corpus cavernosum is a relatively rare event and caused by a sudden increase in intracorporeal pressure due to an external force tearing the thinned tunica albuginea of the erect penis (1,2). Among the typical symptoms are a cracking sound, rapid swelling, discoloration and distortion. Thus the condition is easily diagnosed, but hematoma and swelling often prevent accurate localization of the site of the rupture (1,3). We report the findings of a penile fracture on ultrasonography (US) and magnetic resonance imaging (MRI), techniques which have been employed to investigate patients with this condition.

CASE REPORT

A 41-year-old man was admitted to our hospital with pain and swelling of the penile shaft. The patient denied having sexual intercourse but stated hearing a cracking sound during a morning erection fifteen days ago when he rolled over in bed. The physical examination revealed a subcutaneous mass 2 cm in diameter in the right penile radix consistent with a hematoma. Voiding was normal without hematuria. Physical findings being limited, an ultrasound (US) and MRI were done.

The US of the penis, performed with a 7.5 MHz transducer, showed a well-defined, mostly cystic, loculated, complex mass 2 cm in diameter on the right side of the penile shaft. This was thought to be most consistent with a sub acute hematoma. In addition, a small discontinuity in the tunica albuginea was suggested (Fig. 1).

The MRI was done with a 1.5 T high field magnet. Sagittal and axial T1 and T2-weighted spin echo images, obtained with a high resolution surface coil, showed a 5 mm defect of the tunica albuginea on the right side of the penis associated with a sub acute subcutaneous hematoma (Fig. 2).

The patient was operated; the hematoma was evacuated and the tear in the tunica albuginea was repaired. One month after surgery, erection was normal, without any pain or angulation of the penis.

DISCUSSION

Fractured penis, the most commonly used term to describe a rupture of the corpus cavernosum is a misnomer. The penis in humans is entirely soft tissue and not subject to fracture in the usual sense of the word. The sequelae of rupture results from a tear in the tuni-

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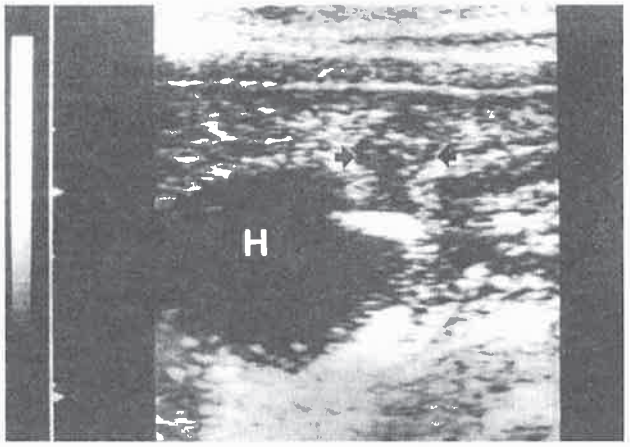

Figure 1. Longitudinal ultrasound scan of penis shows discontinuity of tunica albuginea in the area of tear (arrows) and hematoma (H) adjacent to it.

ca albuginea, which can only occur in the erect state, when the tunica is thinner and tauter than when the penis is flaccid (2). The majority of injuries occur during vigorous sexual intercourse, or because of nonphysiological bending of the penis during self-manipulation or rolling over in bed with a penis in erection (1).

Diagnosis can generally be made on the grounds of a routine history and typical findings, rendering additional procedures unnecessary. However, a case history is not always reliable, and some cases are atypical. In addition, there are situations in which the clinical diagnosis may be false positive. In many patients, a radiological approach is needed to complement the clinical diagnosis for two reasons. Firstly, superficial penile trauma, which is typically only conservatively treated, should be excluded. Secondly, the exact localization and severity of the rupture are of extreme importance to the urologist, because a long incision and a wide dissection or complete degloving of the penis can be avoided if an accurate assessment of the rupture site can be made (1).

Before the advent of US, the corpus cavernosonography was used to assess tunica albuginea tears (4,6). However, it cannot be done in patients who are allergic to iodinated contrast media. There are also risks of priapism, infection, and further formation of hematomas (2,5).

In 1983, Dierks and Hawkins first described the use of ultrasonography for the evaluation of a corpus cavernosum rupture (7). As a non-invasive method without risk of infection, the US can demonstrate hematomas, the exact site of the tear in the tunica albuginea, and define the extent of the injury in most patients. However, small tears can be difficult to detect on the US owing to a blood clot filling the defect and making it almost isochoric with the surrounding normal tunica albuginea (5).

Reports on the use of MRI in the study of penile abnormalities are rare. A good visualization of the soft tissue pathological processes is one of its most obvious advantages. The few reported results of MRI use in the evaluation of penile fractures are promising (1,3).

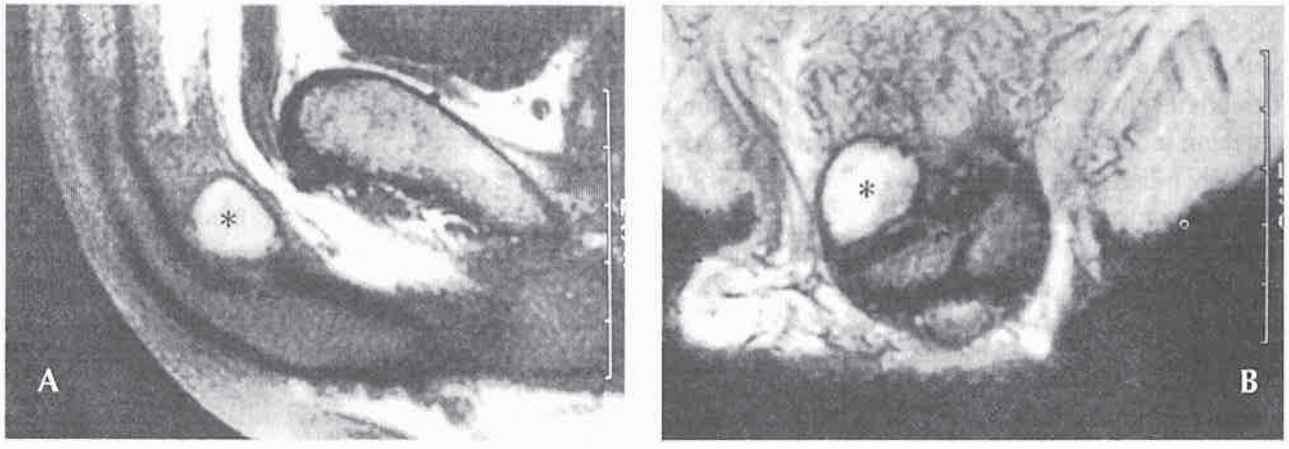

Figure 2. Sagittal T1-weighted (A) and axial T2-weighted (B) spin echo MR images show obvious discontinuity of the low signal intensity layer of tunica albuginea (arrowhead), above which lies the subcutaneous hematoma of heterogeneous high signal intensity consistent with sub acute stage (asterix).

MRI offers the ability to demonstrate penile anatomy in three orthogonal planes. Use of a surface coil yields a particularly impressive contrast and anatomical resolution with an excellent display of the pendulous portion of the penis. The tunica albuginea has a low signal intensity compared to the high signal intensity of the corpora cavernosa and spongiosum. The discontinuity of the tunica albuginea may be demonstrated better on T1-weighted images. Hematomas show a nonhomogeneous, high signal intensity on T1 and T2-weighted spin echo images. The image contrast improves after the use of gadolinium-DTPA (1,3). In our case, a tear in the tunica albuginea with an accompanying hematoma was accurately diagnosed and precisely located on T1-weighted images, and confirmed during surgery.

In summary, penile fracture is an emergency and early surgical intervention is imperative to prevent later complications. The diagnosis of penile fracture does not require further investigation when the patient presents with typical symptoms and physical findings. However, not all patients give an accurate history and present with typical signs of this condition actually have a fractured penis. An US can show the discontinuity of the tunica albuginea in the area of tear and the precise cross-sectional anatomic detail of the hematoma. Although it is too costly for a routine diagnosis of suspected penile fracture, the MRI is helpful in borderline cases.

REFERENCES

1. Fedel M, Venz S, Andreessen R, Sudhoff F, Loening SA. The value of magnetic resonance imaging in the diagnosis of suspected penile fracture with atypical clinical findings. J Urol 1996; 155:1924-1927.
2. Forman HP, Rosenberg HK, McCrum Synder III H. Fractured penis: sonographic aid to diagnosis. AJR 1989; 153:1009-1010.
3. Rahmouni A, Hoznek A, Duran A, Colombel M, Chopin DK, Mathieu D, Vasile N. Magnetic resonance imaging of penile rupture: aid to diagnosis. J Urol 1995; 153:1927-1928.
4. Pliskow RJ, Ohme RK. Corpus cavernosonography in acute "fracture" of the penis. AJR 1979; 133:331-332.
5. Koga S, Saito Y, Arakaki Y, Nakaruma N, Matsuoka M, Saita H, Yoshikawa M, Ohyama C. Sonography in fracture of the penis. Br J Urol 1993; 72:228-229.
6. Karadeniz T, Topsakal M, Arman A, Erton H, Basak D. Penile fracture: differential diagnosis, management and outcome. Br J Urol 1996; 77:279-281.
7. Dierks PR, Hawkins H. Sonography and penile trauma. J Ultrasound Med 1983; 2:417-419.

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REVERSIBLE DIABETES MELLITUS DUE TO PANCREATIC TUBERCULOSIS

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SUMMARY

A 55 year old woman with a one year history of diabetes mellitus presented herself for the evaluation of a pancreatic mass. She had been suffering from severe constitutional symptoms for 12 months, including jaundice, anorexia, vomiting, weight loss, increasing fatigue, night sweats, and recurrent fever attacks of up to 38 °C. An ultrasound and a computed tomography demonstrated an enlargement of the pancreas. A PPD skin test was positive, and the chest x-ray was normal. A laparotomy was performed because pancreatic head carcinoma was highly suspected. The diagnosis of tuberculosis was subsequently confirmed by positive cultures and histological sampling. A quartet of anti-tuberculosis drug therapy was effective in alleviating the symptoms and she remains well 13 months after the initiation of treatment. A follow-up CT, ultrasonography and biochemical investigations revealed a normal pancreas. In conclusion, the masses which form as a consequence of tuberculosis, should be taken into consideration in the differential diagnosis of pancreatic masses. If diabetes has developed in these patients, it should be kept in mind that diabetes may be cured by medical treatment that does not include surgery.

Key words: *Pancreatic disease, tuberculosis, diabetes mellitus.*

ÖZET

Pankreatik Tüberküloza Bağlı Geçici Diabetes Mellitus

55 yaşında bir yıllık diabetes mellitus öyküsü olan kadın hasta pankreatik kitle nedeniyle incelemeye alındı. 12 aydır süregelen sarılık, iştahsızlık, kusma, kilo kaybı, halsizlik, gece terlemeleri, 38∞C ateş gibi ciddi semptomlardan şikayetçiydi. Ultrasonografi ve bilgisayarlı tomografide pankreasta büyüme saptandı. PPD deri testi pozitifti. Akciger grafisi normaldi. Pankreas başı karsinomu şüphesi nedeniyle hastaya laparotomi uygulandı. Histolojik örnekleme ve pozitif kültür sonuçları ile pankreatik tüberküloz tanısı konuldu. Dörtlü antitüberküloz tedavisi ile semptomlarda gerileme sağlandı. Tedavinin başlamasından sonraki 13 ayda hastada belirgin iyilişme gözlendi. Kontrol tomografi, ultrasonografi ve biyokimyasal tetkiklerde normal pankreas görünüm ve fonksiyonları tespit edildi. Sonuç olarak pankreatik kitlelerin ayırıcı tanısında tüberküloz sonucu oluşabilen kitlelerde gözönüne alınmalıdır. Eğer bu hastalarda diabet gelişmişse diabetin cerrahi olmaksızın tıbbi tedavi ile düzeltilebileceği akılda tutulmalıdır.

Anahtar kelimeler: *Diabetes Mellitus, Pankreatik hastalık, Tüberküloz.*

Tuberculosis remains one of the most prominent health care problems in underdeveloped and developing countries. However, extra-pulmonary presentations of tuberculosis are not commonly observed in these countries. Among those extra-pulmonary presentations that are seen, pancreatic tuberculosis is very rarely observed, and the diagnosis is difficult to make in general. Pancreatic tuberculosis might commonly mimic pancreatitis, a pancreatic abscess and pancreatic cancer. A differential diagnosis of pancreatic cancer might only be made upon the performance of a laparotomy(1, 2, 3).

Diabetes mellitus (DM), on the other hand, is commonly observed disease that can be a result of various factors. DM is, in general, associated with genetic and environmental factors. Infrequently, DM secondary to various infections involving the pancreas may be observed (4). However, the presence of overt DM associated with pancreatic tuberculosis, and the correction of the clinical situation through medical and surgical

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interventions, is very rare. Here we present just such a patient who, at one year following the diagnosis of DM with abscessed pancreatic tuberculosis, experienced an overt correction of DM.

CASE REPORT

A 55 year-old female with eight children had been followed up in the Department of Endocrinology for one year with the diagnosis of DM. On the first admission, her fasting blood glucose level was 237 mg/dL and the HbA_{1C} level was 8.7 %. Her blood glucose level had been rgulated on a diabetic diet and 160 mg of gliclazide (fasting blood glucose level: 110 mg/dL, HbA_{1C}: 7.4%). She was readmitted with complaints of fatigue, which had increased over the previous six months, a loss of appetite, weight loss (8 kilogram over six months), a feeling of epigastric fullness, fever, and abdominal pain. Her physical examination revealed a lean woman (height:1.63 m, body weight: 52 kg). Her body temperature was 37.8 °C, the pulse rate was 82 /min and the arterial blood pressure was 115/70 mmHg. Epigastric tenderness and a left sided mass lesion were observed. The erythrocyte sedimentation rate (ESR) was 102 mm/h, the white blood cell count was 9600/mm3, the hemoglobin level was 10.2 g/dL, the fasting blood glucose level was 130 mg/dL, the postprandial blood glucose level at 2 hours was 153 mg/dL, the carcinoembryonic antigen (CEA) level was 1.87 ng/ml(n: 3-5 ng/ml), alpha-fetoprotein level was 0.90 U/ml(n: 5<U/ml) and carbohydrate antigen (CA 19.9) level was 2.91 U/ml (n:<14 U/ml). Other laboratory investigations were normal. An ultrasound revealed a 7.5x2.5x4.5 sized mass with lobulated contours located in the head of the pancreas. Upon the observation of a 7x4 cm lobulated mass with a heterogeneous echo pattern on the abdominal CT (Figure 1), the decision to operate was made based on the presumptive diagnosis of pancreatic cancer. During the operation, the mass lesion was found to diffusely involve the pancreas, the head in particular, and to compress the portal vein and the cystic duct. A frozen section of the mass lesion was reported as a granulomatous inflammatory process. The abscess localized in the head was drained and samples were obtained for cultures and antibiograms. A lymph node sampling was followed by a cholecystectomy. The bacterial evaluation was negative for aerobic and anaerobic microorganisms. The lymph node samples were reported as "tuberculous lymphadenitis". The histopathological evaluation of the resection material revealed a typical presentation of tuberculosis in various areas (Figure 2). The PPD examination was found to be positive (23 mm). Anti-tuberculosis treatment with streptomycin, pyrazinamide, rifampin, and isoniazid was administered and was followed by a consolidation treatment with rifampin and isoniazid, at two months. At four months of treatment, the ESR was 45 mm/h, the white blood cell count was 5400 mm^3, the hemoglobin level was 13.1 g/dL, the fasting blood glucose level was 96 mg/dL and the HbA_{1C} level was 6.9 %. A mass lesion of 4.5x3 cm was detected in the head of pancreas on an abdominal ultrasound. Gliclazide was

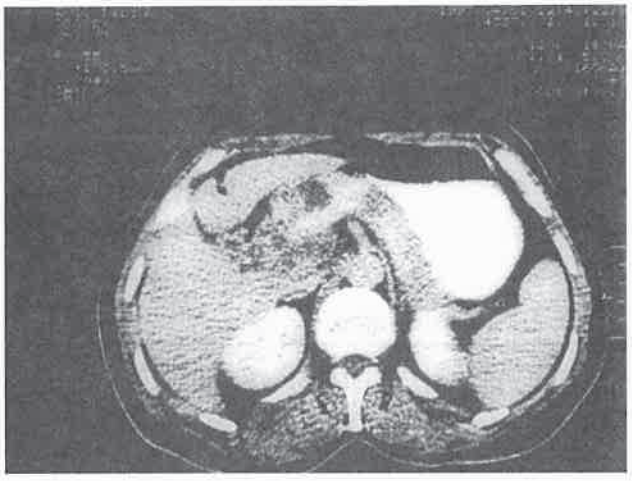

Figure 1: Lobulated mass lesion with heterogenous echo pattern on abdominal CT.

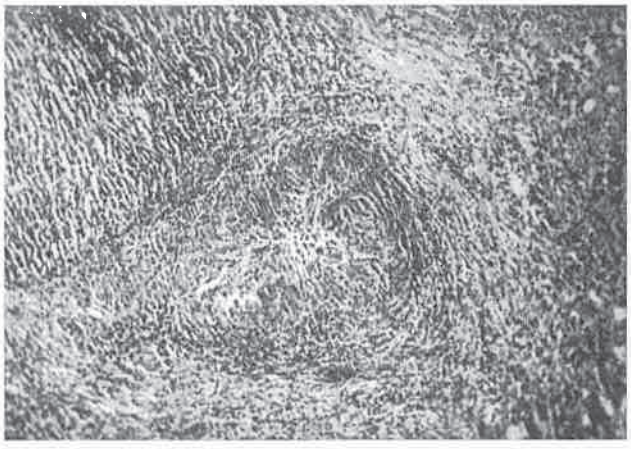

Figure 2: Histopathological evalvation of the resection material revealed typical presentation of tuberculosis.

discontinued and an ordinary diet was resumed upon the normalization of the blood glucose level and the HbA_{1C}. Insuline and C peptide responses were evaluated with the oral glucose tolerance test (OGTT).

After eight months of treatment, the patient was back to her normal body weight and the ESR was 24 mm/h., the blood glucose level and the HbA_{1C} (6.2%) were normal, despite an unrestricted diet and the absence of anti-diabetic medications. In an abdominal CT scan, the pancreatic mass had regressed (Figure 3). A repeat OGTT revealed a normal blood glucose response, in contrast to the prior OGTT.

After one year of treatment, all signs and symptoms were normalized and the anti-tuberculosis treatment was discontinued. An abdominal ultrasound was normal, apart from a mild irregularity on the head of pancreas. The patient is on an ordinary diet and is not on any anti-diabetic management medication.

DISCUSSION

The incidence of tuberculosis is progressively increasing in developing countries as well as in the developed countries, in accordance with waves of migration and epidemics of AIDS (4). Similarly, tuberculosis of the extra-pulmonary sites, and abdominal tuberculosis in particular, is increasing in number (5). Yet pancreatic tuberculosis is rare. Different series have reported the frequency of pancreatic tuberculosis in 4.7%, 2.1% and 1.4% of autopsies (6, 7, 8), whereas Lundstedt et al. have reported only three cases of pancreatic tuberculosis in their series of 112 cases of abdominal tuberculosis (5).

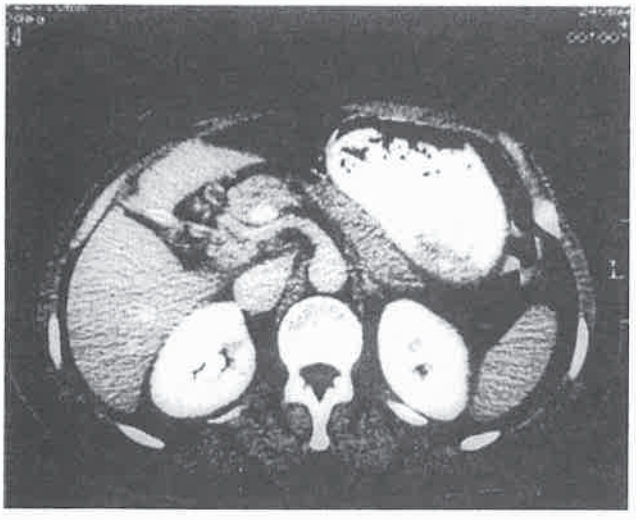

Figure 3: At eight months of treatment, on abdominal CT, the pancreatic mass lesion regressed.

Pancreatic tuberculosis may present with various signs and symptoms, including acute and chronic pancreatitis, biliary obstruction, a mass lesion mimicking pancreatic cancer, and massive gastrointestinal system bleeding associated with pancreatic involvement and arterial invasion (1-3, 9-10-14). Abscessed pancreatic tuberculosis is very rare with only a few cases reported in the literature (11, 14-18).

Pancreatic tuberculosis might result either from the hematogenous spread in the form of miliary tuberculosis or the spread from the lymph nodes, the splenic flexure or the duodenum (10, 19). In our case, pulmonary tuberculosis had not been diagnosed, (upon clinical history and examinations), and had spread to the pancreas and it was assumed to have originated from the neighboring lymph nodes. The observation of lymphadenopathy in association with the pancreatic lesions on both the CT scan and the laparotomy, as well as tuberculous lymphadenitis reported in the histo-pathological examination, are in support of this assumption.

Tuberculosis leading to a mass lesion and abscess formation in the pancreas may mimic pancreatic cancer and, therefore, the decision for an operation is made. Similarly, the decision to operate was made, based upon the presumptive diagnosis of pancreatic cancer in our case, and the diagnosis of tuberculosis was made during the operation.

The most striking feature of our case is the complete correction of DM that had been regulated with oral anti-diabetics upon the initiation of anti-tuberculosis treatment. Prior to the operation, the blood glucose level had been regulated while the patient was on a diabetic diet and on 160 mg gliclazide, whereas after four months of treatment, the blood glucose level and the HbA_{1C} were within the normal range while the patient was on a diabetic diet, but not on any oral anti-diabetic medication. However, a diabetic curve was obtained upon the OGTT after four months of treatment. After eight months of treatment, the blood glucose level and the HbA_{1C} were normal, despite the fact that the patient had resumed an ordinary diet and was not taking any oral anti-diabetic medication. The OGTT after eight months of treatment did not reveal a diabetic curve. Anti-tuberculosis treatment was dis-

continued after one year and repeated CT scans demonstrated that the pancreatic mass had almost disappeared The blood glucose and HbA_{1C} levels had returned to normal.

In an analysis of the literature, we have not seen a case of abscessed pancreatic tuberculosis that has been initially followed up with the diagnosis of DM in which the DM subsequently disappeared completely after anti-tuberculosis treatment. We conclude that tuberculosis should be kept in mind in the differential diagnosis of pancreatic masses and that DM might be completely corrected in these patients if it exists in the absence of other genetic and environmental factors.

REFERENCES

1. Chandrasekhara KL, Iyer SK, Stanek AE, Herbstman H: Pancreatic tuberculosis mimicking carcinoma. Gastrointestinal Endoscopy 31:386-8, 1985.
2. Kitai IC, Harid AC, Matengo JA: Tuberculosis of the pancreas mimicking carcinoma: Report a case. Central African J Med 33:20-22, 1987.
3. Dhall JC, Bishnoi PK, Dalal AK, Marwah S, Goel R, Marwah N, Dhall A: Tuberculosis of the pancreas: A clinical rarity. Am J Gastroenterol 92:172, 1997
4. Berson BD, Mendelson DS, Janus CL: Tuberculosis abscess of the pancreas in AIDS: CT findings. Mt Sinai J Med 56:297-9, 1989.
5. Lundstedt C, Nyman R, Brismar J, Hugosson C, Kageri I: Imaging of the tuberculosis: Abdominal manifestations in 112 patients. Acta Radiologica 37:489-95, 1996.
6. Aurbach O: Acute generalized miliary tuberculosis. Am J Pathol 20:121-36, 1944.
7. Paraf A, Menofer C, Texier J: La tuberculose du pancreas et la tuberculose des ganglions de l'etage superieur de l'abdomen. Rev Med-Chir Mal Foie 41: 101-26, 1966.
8. Gelb AF, Leffler C, Brevin A, et al: Miliary tuberculosis. Am Rev Respir Dis 108:1327-33, 1973.
9. Rushing JL, Hanna CL, Selecky PA: Pancreatitis as the presenting manifestations of miliary tuberculosis. West J Med 129: 432-36, 1978.
10. Stock KP, Riemann JF, Stadler W, Rosch W: Tuberculosis of the pancreas. Endoscopy 31:178-80, 1981.
11. Crowson Mc, Perry M, Burden E: Tuberculosis of the pancreas: A rare cause of obstructive jaundice . Br J Surg 71:239, 1984.
12. Desai DC, Swaroop VS, Mohandas KM, Barges A, Dhir V, Nagral A, Jagonnath P, Sharma OP: Tuberculosis of the pancreas: Report of three cases. Am J Gastroenterol 86: 761-3, 1991.
13. Takhtani D, Gupta S, Suman K,Kakkar N, Challa S, Wig JD, Sun S: Radiology of pancreatic tuberculosis: a report of three cases. Am J Gastroenterol 91:1832-4, 1996.
14. Fans T, Yan KW, Lau WY, Wong KK: Tuberculosis of the pancreas: A rare cause of massive gastrointestinal bleeding. Br J Surg 73:373, 1986.
15. Crook LD, Johnson FP: Tuberculosis of the pancreas: A case report. Tubercle 69:148-51, 1988.
16. Sözbilen M, Erhan Y, Koyuncu A: Tuberculosis pancreatic abscess. Br J Surg 79:802, 1985.
17. de Miguel F, Beltron J, Sabas JA, Sadaba F, Santamaria JM, Bustamante V: Tuberculous abscess of the pancreas. Br J Surg 72: 438, 1985.
18. Stambler JB, Klinaber MI, Bliss CM, Lamont JT: Tuberculous abscess of the pancreas. Gastroenterology, 83:922-25, 1982.
19. Crofton J, Horne N, Miller F(Eds): Clinical Tuberculosis. 130-32, Hong Kong, MacMillan, 1992.

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TEMPOROMANDIBULAR JOINT PAIN SYNDROME; DYSFUNCTION AS A DIFFERENTIAL DIAGNOSIS IN CASE OF EAGLE'S SYNDROME

Ali Teoman Tellioğlu* • İbrahim Tekdemir**

SUMMARY

We presented the case of a patient with Eagle's Syndrome, which had better was referred for temporomandibular joint (TMJ) pain dysfunction syndrome in a review of the literature, we discovered the importance of a intra-oral examination for making a differential diagnosis for the TMJ pain dysfunction syndrome.

Key words: *Styloid process, Eagle's Syndrome, temporomandibular joint pain*

ÖZET

Temporomandibularis ağrısına neden olan Eagle sendromunun farklı teşhisi

Çalışmamızda Eagle sendromuna bağlı olarak gelişen art. temporomandibularis ağrısının tanısının konulmasında farklı teşhis yöntemlerinin dışında intraoral muayenenin önemi ortya konulmuş ve literatür bulgularıyla karşılaştırılmıştır.

Anahtar Kelimeler: *Proc. styloideus, Eagle Sendromu, Art. temporomandibularis*

The elongation of the styloid process has been well reported previously as a source of pain in the cervicofacial region (1). This condition, known as "Eagle's Syndrome", is characterized by a dull, nagging pain localized in the throat . There may be some difficulty in swallowing, and considerable pain may occur during while swallowing. However, Eagle's Syndrome can be confused with several other disorders and then patients who are with misdiagnosed may suffer from Eagle's Syndrome even when the patient has tried to seek treatment for this problem for a long time. Therefore, surgeons should be aware of facial pain disorders and Eagle's Syndrome should be kept in mind as a possible alternative diagnosis in apparent cases of TMJ. We present a case of Eagle's Syndrome, which was referred to us for TMJ pain dysfunction Syndrome. We would also like to point out the importance of an intraoral examination for a differential diagnosis of TMJ Pain Dysfunction Syndrome.

CASE REPORT

A 50-year-old women was referred for Temporomandibular Joint Pain Dysfunction Syndrome from the Ea, Nose, Throat clinic. She reported that she had undergone several treatment attempts with occusal splints by dentists.

The patient reported that she had experienced severe pain in her left ear and in the preauricular area. She also had difficulty in swallowing. The patient gave a history of a thyroidectomy 7 years ago. The clinical examination revealed some limitation of the opening mouth. No other extra-oral signs were present. Intra-orally there was poor dentition. During the palpation of the left tonsillar area, a bone like protuberance was detected. A panaromic radiograph showed an elongated left styloid process (Figure 1). The diagnosis of Eagle's Syndrome was then confirmed and made. The patient did not agree to the surgical treatment and found relief from her symptoms with a soft diet and a

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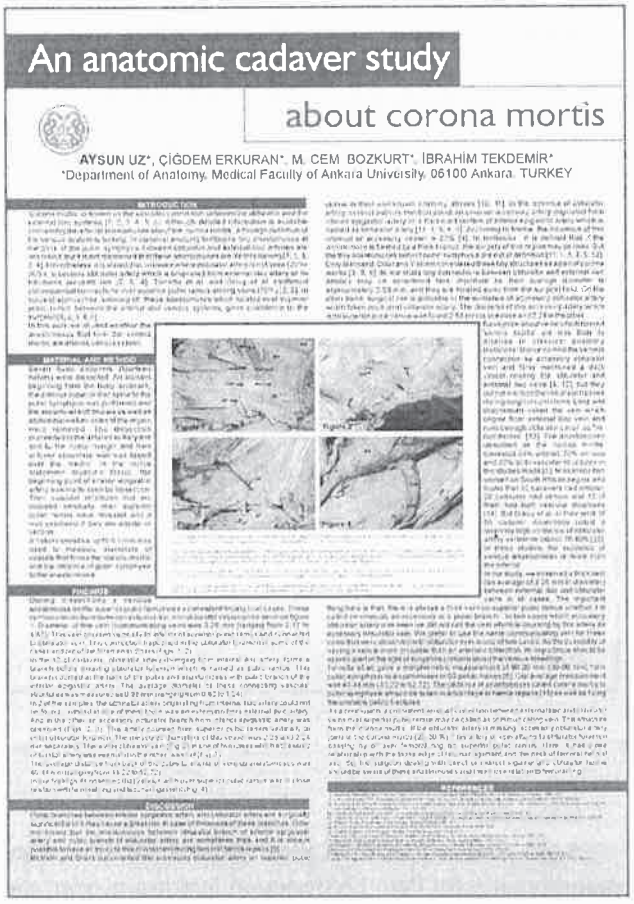
An anatomic cadaver study

about corona mortis

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Figure 1: A panoramic radiography shows a elongated styloid process on the left side with a normal styloid process on the right side.

nonsteroid antiinflamatory agent. No recurrence of her symptoms was noted at 6 months when she was not to follow up.

DISCUSSION

The styloid process is a slender, cylindiric bony structure placed immediately in front of the stylomastoid foramen and fused to the inferior aspect of the temporal bone .It normally lies between the internal and external carotid arteries. Three muscles and two ligaments originate from styloid process (2). The stylopharyngeous muscle arises near it's base from the medial and slightly posterior aspect, the stylohyoid muscle arises from the posterior and lateral aspect near the middle, and the styloglossus muscle arises from the anterior terminal portion. The tip of the styloid process is continuous with the stylohyoid ligament . The mean radiographic length of the styloid process has been reported to be between 20-30 mm long (3,4). The styloid process originates from Reichert's cartilage, a structure of the second branchial arch origin, which has four divisions: the tympanohyale, stylohyale, ceratohyale, and the hypohyale . During the first 8 years of life the tymponohyale calcifies to form the base of the styloid process. The stylohyalene portion exhibits the greatest variation in the degree of degeneration. If calcification of the stylohyale portion occurs, then a long styloid process results. If not, a short styloid occurs. The remaining portions, the cerotohyale and the hypohyale divisions, do not contribute to the styloid process. In utero, the ceratohyale portion degenerates and forms the stylohyoid ligament. The hypohyale fuses with the third branchial cartilage and becomes the lesser cornu of the hyoid bone. The failure of degeneration and the subsequent calcification of portions of the Reichert's cartilage may result in an elongated styloid or a lesser cornu of the hyoid, the calcification of the stylohyoid ligament or, rarely, a solid bar of bone from the styloid to the hyoid bone (5). Histologic and microradiographic techniques have not identified any evidence of post-natal elongation of the styloid (6).Calcification of the soft tissue surrounding the styloid does occur, but results only in an increase in the diameter of the styloid, not in the length.Eagle reported two cases of an elongated styloid process leading to pain in the ear region and within the throat (1). Subsequently, Eagle described a variety of symptoms including discomfort in swallowing , headache, severe hemi-facial pain, sore throat, and glossodynia (7,8,9). He distinguished between two types of the syndrome. The classic type occurs immediately after a tonsillectomy due to surgical exposure, and the second type, due to an elongated styloid process. The normal styloid process is considered to be no longer than 30 mm in length (3). However in some cases, the styloid process may be up to 8 cm (10). The elongated process impinges carotid arteries and produces an irritation of the sympathetic nerves in the arterial sheet. (3). Finally, the resulting impairment of blood flow is responsible for neck and facial pain in the areas dependent on the vessel affected. The styloid syndrome is more frequent in women than in men (11).It is often observed in patients of 30 years or older (8). Bilateral involvement is quite common, diagnosed by either palpatorily or radiologically (3,12). The differentional diagnoses of a symptomatic elongated styloid process

includes the following criteria: 1. cranial nerve neuralgias like trigeminal neuralgia 2. temporomandibular joint disease 3. chronic pharyngotonsillitis 4. unerupted or impacted molar teeth 5. faults of dental prostheses , and 6. tumors pharyngeal and base of the tongue (13). Nonsurgical and surgical treatment alternatives can be used for the treatment of Eagle's Syndrome. Nonsurgical treatment includes nonsteroidal anti-inflamatory agents and transpharyngeal injections of steroids (5). However the ffective treatment for eliminating symptoms is the surgical shortening of the elongated styloid process. The intra-oral and the extra oral approaches are the two well accepted routes to reach the process (13).

The symptoms of TMJ pain dysfunction syndrome basically includes pain in the pre-auricular region, a limited mandibular opening and occasional popping and clicking during jaw movements (14). Malocclusion and long term microtrauma cause masticatory muscle spasms and it is therefore referred to as myofacial pain dysfunction syndrome (15). There is no abnormality on plain radiographs in the majority of patients with TMJ pain dysfunction syndrome (15,16). It was reported that 10 % of the cases of Eagle's Syndrome have mimic the symptoms of TMJ pain dysfunction syndrome (17). It is also described that Eagle's syndrome can be confused with TMJ pain dysfunction syndrome (5).Treatment of misdiagnosed patients causes unsatisfactory results and the patient, suffering for months or even years from symptoms related to Eagle's Syndrome is frequently emotionally labile and often seems neurotic (17). However, a differentional diagnosis can be determined between TMJ pain dysfunction syndrome and Eagle's Syndrome by performing an intra-oral examination. Furthermore x-rays, especially panoramic radiographs are very useful for the distinguishing between these two pathologies. Finally, an intra-oral examination can easily be performed in order to eliminate Eagle's Syndrome. Therefore surgeons should perform a palpation of the tonsillar fossa during an examination for TMJ pain dysfunction syndrome, and Eagle's syndrome must be considered as a differentional diagnosis for TMJ pain dysfunction syndrome.

REFERENCES

1. Arıncı K, Tekdemir İ, Fidan G, Dağlı Ş, Köse K: Proc. Styloideus varyasyonları. Türk Tıp Araştırma Dergisi, 1992, 10:306-309.
2. Monsour PA, Young WG:Variability of the styloid process and stylohyoid ligament in panoramic radiographs. Oral Surg Oral Med Oral Pathol. 1986, 61:522-26.
3. Koufman SM, Elzay RP, Irish EF, Richmond V: Styloid process variation. Radiologic and clinical study. Arch Otolaryng 1970, 91:459-63.
4. Stafne EC, Hollinshead WH: Roentgenographic observations on the sthylohyoid chain. Oral Surg Oral Med Oral Pathol .1962, 15:1195-12002.
5. Baogh RF, Stocks RM:Eagle's Syndrome: a reappraisal ENT Journal 1993, 75:341-344.
6. Lengele B, Dhem A Microradiographic and histological study of the styloid process of the temporal bone. Acta Anat 1989, 135:193-199.
7. Eagle WW: Elongated styloid processes: further observations a new syndrome. Arch Otolaryngol. 1948, 47:630-640
8. Eagle WW: Symptomatic elongated styloid process: report of two cases of styloid process-carotid artery syndrome with operation. Arch Otolaryngol 1949, 49:490-503.
9. Eagle WW: Elongated styloid process: symptoms and treatment. Arch Otolaryngol. 1958, 67:172-176.
10. Rath G, Anand C: Abnormal styloid process in a human skull. Surg Radiol Anat.1991, 13:227-229.
11. Harma R :Stylalgia.: clinical experiences of 52 cases. Acta Oto Suppl 1967, 24:49-53.
12. Steurman EP: Styloid Syndrome in absence of elongated process. Acta Otolaryngol .1968, 66:347-56.
13. Zohar Y, Strauss M, Laurian N:Elongated styloid process syndrome: inraoral versus external approach for styloid surgery. Laryngoscope 1985, 95:976.-79.
14. Mendes D, Jacobs J: Traumatic deformities and reconstruction of the temporomandibular joint. n: Cohen M Mastery of plastic and reconstructive surgery, New York, Little, Brown and Company 1994, p 1220.
15. Laskin DM: Etiology of the pain-dysfunction syndrome. J Am Dent Assoc. 1969, 9:147.
16. Stanson AW, Baker HL : Routine tomography of the temporomandibular joint. Radiol Clin North Am. 1976, 14:105.
17. Barrett AW, Griffiths MJ, Scully C: Osteoarthrosis, the temporomandibular joint, and Eagle's Syndrome. Arch Otolaryngol 1993, 75:273-75.
18. Russell TE: Eagle's syndrome: diagnostic considerations and report of case JADA. 1997, 94:548-50.

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ANGIOMYOLIPOMA OF THE KIDNEY WITH LYMPH NODE INVOLVEMENT*

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SUMMARY

Angiomyolipoma is an uncommon benign tumor accounting for less than 1% of all surgically excised tumors of the kidney. Here we report a case of aggressive renal angiomyolipoma with regional lymph node involvement in a 27-year-old man with a unilateral renal mass. Grossly the tumor was a well delineated yellow-gray mass with central hemorrhage. Microscopically it was composed of mature adipose tissue showing variations in cellular size and nuclear appearance, convolutes of thick walled blood vessels and irregularly arranged sheets of smooth muscle often showing a prominent perivascular arrangement.

Although the histologic appearance of this tumor is quite characteristic, it is sometimes misdiagnosed as liposarcoma or leiomyosarcoma because of its large size, focal cellularity, cellular pleomorphism, and occasional growth of the tumor in lymph nodes. Despite these atypical features, nearly all angiomyolipomas pursue a benign clinical course, and demonstration of regional lymph node involvement can only be regarded as evidence of focal aggressive behaviour and not necessarily of malignancy.

Key words: *Angiomyolipoma, lymph node involvement*

ÖZET

Lenf Nodu Tutulumu Gösteren Renal Anjiomyolipoma

Anjiomyolipoma cerrahi olarak çıkartılan tüm böbrek tümörlerinin %1'den azının oluşturan nadir bir benign tümördür. Burada tek taraflı renal kitlesi olan 27 yaşındaki erkek hastada saptanan ve bölgesel lenf nodu metastazı gösteren agresif bir renal anjiomyolipoma olgusu sunulmuştur. Tümör makroskopik olarak iyi sınırlı, santral hemoraji bulundural gri-sarı renkli bir kitle görünümündeydi. Mikroskopik olarak tümör, hücresel boyut ve nükleer görünüm açısından değişkenlik gösterebilen matür yağ dokusu ile karışık kalın duvarlı damarlar ve genellikle belirgin perivasküler düzenlme gösteren düz kas hücrelerinin oluşturduğu düzensiz demetlerden meydana gelmekteydi.

Bu tümörün karakteristik bir histolojik görünümü olmasına karşın bazen büyük boyutu, fokal sellüleritesi, hücresel pleomorfizmi ve nadir lenf nodu tutulumu nedeniyle bazen liposarkoma veya leiomyosarkoma şeklinde yanlış tanı alabilmektedir. Bu atipik özelliklere rağmen hemen tüm anjiomyolipomalar benign klinik seyir gösterirler. Lenf nodu tutulumunun saptanması lokal agresif davranışı ifade etmeli, malignite yönünde değerlendirilmelidir.

Anahtar Kelimeler: *Anjiomyolipoma, lenf nodu tutulumu*

Lymph node involvement of a neoplasm distant from primary site is usually considered an evidence of malignancy. However, a few benign tumors such as endometriosis and "benign metastasizing" leiomyoma are exceptions to this general rule (1). Angiomyolipoma (AML), a benign renal tumor, has also been reported to cause nodal and even splenic involvement. These instances have been explained by the multicentricity of the tumor rather than its malignant potential (1-5). Herein we report a case of renal angiomyolipoma with concurrent lymph node involvement.

CASE REPORT

A 27-year-old man underwent left radical nephrectomy with a clinical diagnosis of renal adenocarcinoma presenting as left flank pain, progressively enlarging loin mass and hematuria. An abdominal CT scan demonstrated a mixed solid and cystic mass in the left kidney, which only focally contained fat. The nephrectomy specimen consisted of the kidney with attached perirenal fat, a segment of ureter, and a segment of renal artery. The cut surface of the specimen revealed a solid mass measuring 13x7x3 cm with pushing

* This case report was presented as a poster at the 2nd Balkan Congress of Oncology held on September 10-14, 1998 in İzmir-Turkey

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borders. The tumor consisted of lobulated, solid, yellow tissue admixed with whorls of gray-white soft tissue (Fig 1). The mass abutted the renal capsule but did not appear to penetrate it.

Microscopically, the mass consisted of a mixture of fat, smooth muscle arranged in fascicles, and thick walled blood vessels (Fig 2). The smooth muscle cells showed focal mild nuclear atypia, but only a few typical mitoses were identified. Some sections consisted largely of adipose tissue; however thick walled blood vessels and bundles of smooth muscle fibers were occasionally present. Four periaortic lymph nodes also contained similar tissue; the tumor was present beneath the subcapsular sinuses and extended into the nodal parenchyme and capsule (Fig 3). The renal artery and ureters were unremarkable.

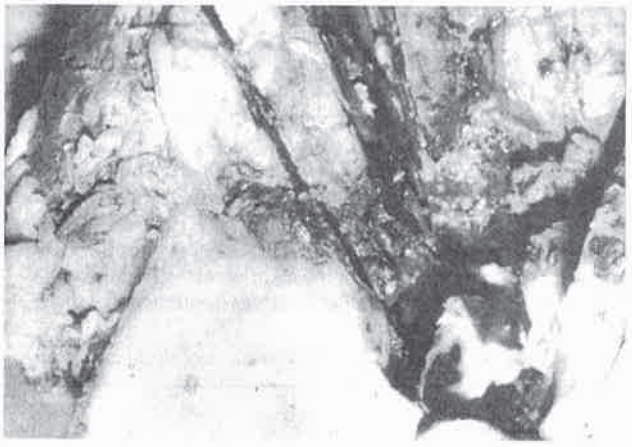

Figure 1: The tumor consisted of lobulated solid, yellow tissue with central focal hemorrhage.

DISCUSSION

AMLs are polymorphic tumors composed of three different tissue components: smooth muscle, blood vessels, and mature adipose tissue (1-7). They are classified as benign hamartomas, and while usually a renal or pararenal neoplasm, they have been described in various locations including the skin, liver, fallopian tube, spermatic cord, penis, vagina, and nasal cavity (7). There is a well established relationship between AML and tuberous sclerosis complex. Approximately 50% of tuberous sclerosis patients harbor an AML, and in half of the cases AML occurs in a background of tuberous sclerosis. Unlike sporadic AMLs which tend to be unilateral and solitary, AMLs associated with tuberous sclerosis are usually small, bilateral and multifocal (3).

Although the presence of neoplastic cells in a lymph node usually indicates metastatic involvement, a few benign tumors or tumor-like lesions may do so without the implication of malignancy. Endometriosis and "benign metastasizing" leiomyoma (leiomyomatosis) are well known examples to benign pathologies having a potential for lymph node involvement. Being a benign renal tumor AML may occur outside the kidney as isolated nodules. There have also been a few reports of lymph node involvement from AML (1,3,4,5).

The malignant potential of AML has long been debated in the literature. In early reports lymph node involvement has been believed to show malignancy.

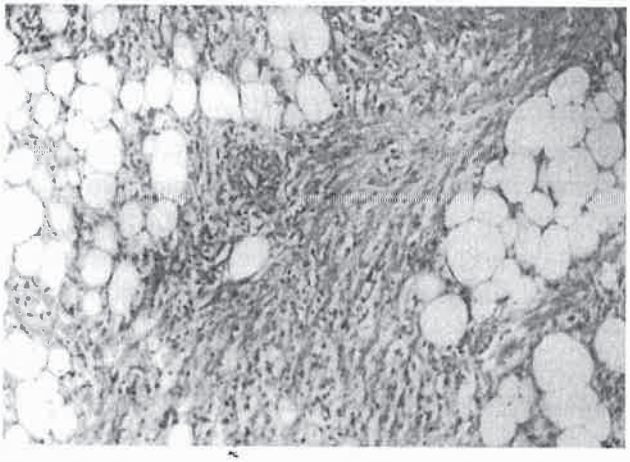

Figure 2: The neoplasm is composed of smooth muscle fibers, adipose tissue, and thick walled blood vessels (H-E, x20).

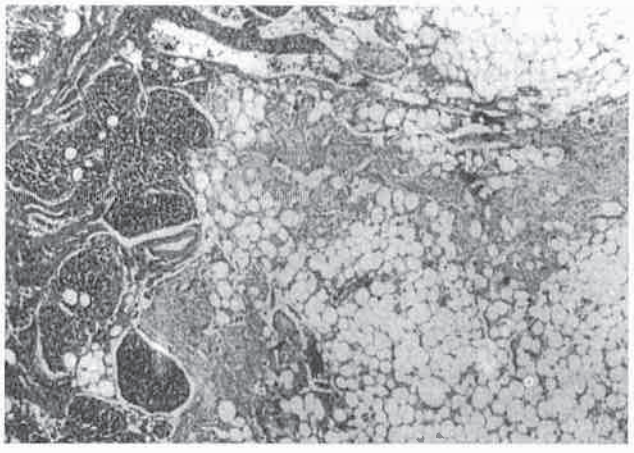

Figure 3: Regional lymph node involved by angiomyolipomatous elements (H-E, x50).

Though perinephric invasion, vascular parasitation, and nodal involvement seem to blur the boundary between benignity and malignancy, these may only form part of the normal behavioral spectrum of this benign neoplasm, since there has been no documented case of distant metastases (1,3,4).

Our patient exemplifies an instance of renal angiomyolipoma with lymph node involvement. This case did not show any other stigma of tuberous sclerosis, which, as mentioned earlier, was reported to accompany half of the cases of AML. The true incidence of lymphatic involvement in AML cannot be assessed. Due to a benign course of these patients on long term follow up, most authors believe the presence of AML in regional lymph nodes is indeed a reflection of multicentricity of this disorder rather than a metastatic event. In accordance with this argument no sign of local or distant metastasis could be detected in our patient for 18 months postoperatively.

Jae et al. performed flow-cytometric DNA analysis in three cases of angiomyolipoma. The primary tumors of the kidneys and tumors in the lymph nodes of all patients contained diploid DNA. The lack of aneuploidy in both the kidney and lymph nodes, although not excluding malignant neoplasia with certainty, supports the benign nature of this lesion (4).

Mohamed et al. performed immunohistochemical analysis in six cases of renal angiomyolipoma. Immunohistochemical analysis revealed positive staining reaction of the vascular and adipose tissue components with HMB-45 antibody in three of the six patients (7). HMB-45 antibody that was originally believed to detect a specific malignant melanoma-associated antigen has more recently been regarded as a relatively nonspecific tumor marker. Thus, AMLs may now be included in a category of neoplasms without evidence of melanotic differentiation but showing HMB-45 immunoreactivity.

Our case was one of the patients with renal angiomyolipoma showing lymph node involvement. Authors believe that presence of angiomyolipoma in regional lymph nodes is a reflection of multicentricity of this disorder and does not represent malignant spread. Of the many cases of renal angiomyolipoma reported to date the only threats to life have been from massive hemorrhage, progressive renal failure or operative mortality. Although malignant change may be a remote possibility, the goal of conservation of normal renal tissue in patients with angiomyolipoma must remain as important as the alleviation of symptoms.

REFERENCES

1. David A, Peter T, Richard M, et al. The significance of nodal involvement in renal angiomyolipoma. J Urol 1982; 128:1292-1295.
2. Merk E, William B, Francis H, et al. Angiomyolipoma with regional lymph node involvement. Human Pathol 1986; 17:962-963.
3. Rober S, David B, Edward R, et al. Renal angiomyolipoma associated with lymph node involvement and renal cell carcinoma in patients with tuberous sclerosis. J Urol 1989; 141:930-932.
4. Jae Y, Alberto G, David J, et al. Angiomyolipoma of the kidney with lymph node involvement. Arch Pathol Lab Med 1990; 114:65-67.
5. Agaral R, Agaral P, Dalela D, et al. Renal angiomyolipoma with nodal involvement. British Journal of Urology 1995; 76:17.
6. Kaiserling E, Kröber S, Xiao J, et al. Immunoreactivity with HMB-45. Histopathol 1994; 25:41-48.
7. Abdulla M, Hai X, Arthur D, et al. Renal angiomyolipoma. Arch Pathol Lab Med 1994; 118: 735-739.