Journal of Ankara Medical School

ISSN 1300–5464

Vol 19, No 3, 1997

Journal of Ankara Medical School

Vol 19, No 3, 1997

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Journal of Ankara Medical School

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Editorial Office:
A.Ü. Tıp Fakültesi Yayın Komisyonu Başkanlığı Sıhhıye-ANKARA

ISNN 1300 - 5464

Typesetting • Design • Print: Öncü Limited, Tel: (0.312) 231 20 26 • Fax: (0.312) 230 73 52

Journal of Ankara Medical School

Published Quarterly by
ANKARA UNIVERSITY MEDICAL SCHOOL

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COPD, PLATELET FUNCTIONS AND N-ACETYL CYSTEINE*

Sema Yavuzer • Gülseren Kayabıyıklıoğu*****
Banu Ocakçıoğlu • Öznur Akkoca*****

SUMMARY

In our department previously it has been determined that in COPD (chronic obstructive pulmonary disease) patients there is oxidant stress, tendency for hypercoagulability and increase in platelet functions.

In the presented study, it was aimed to determine the effect of antioxidant defense supportive treatment on platelet functions. 15 COPD patients were treated by 600 mg/day (3x200 mg) N-Acetyl Cysteine, "ASIST" (Bilim ilaç San. ve Tic. A.Ş) for 3 months and platelet aggregation responses in whole blood to ADP and collagen were examined before and after treatment.

In our study it was observed that N-Acetyl Cysteine treatment decreased the platelet aggregation response induced by collagen significantly ($p<0.05$).

The maximum aggregation rate and maximum aggregation intensities of the platelets were determined by the method of electrical impedance in Chrono-Log Whole Blood Lumi-Aggregometer and the results were evaluated by Student's t Test.

The results of the presented study shows that the increased platelet functions may have an important role in the observed hipercoagulability tendency and thromboembolism and treatment of supporting glutathion system may decrease the risk of thromboembolic complications by regulating the platelet functions.

Key Words: *Chronic Obstructive Pulmonary Disease (COPD), N-acetyl Cysteine (NAC), Platelet aggregation*

The investigations that were made in 1989-1990 in our department showed that oxidant stress might have an important role in pathogenesis of chronic obstructive pulmonary disease (COPD) and suggested that imbalance between exogenous and/or endogenous oxidant radicals and extracellular and intracellular antioxidant systems might be responsible for this disease (1-5).

In COPD patients, thromboembolism is not an unusual finding. Major pulmonary thromboembolism was found in 28 percent of patients with chronic airway obstruction (36 of 128 patients) at autopsy (6). Considering the hypercoagulability tendency that has been seen in these patients, a study aiming to investigate the platelet functions in COPD patients was performed in our department in 1992 (7). Findings of that study clearly showed that there was an increased tendency of aggregation and secretion in platelets which was suggested to be responsible for the observed hypercoagulability and thromboembolism.

There are few literature data about the platelet functions in COPD patients. In addition we could found only one report about the effects of N-acetyl cysteine (NAC) treatment on platelet functions(8). On the other hand it was reported that per oral administration of NAC has been a simple and efficious means of correcting oxidant-antioxidant imbalance (9).

The aim of the presented study is to investigate the effects of NAC therapy on platelet functions in COPD patients.

MATERIAL AND METHODS

15 COPD patients in stable condition who all met the American Thoracic Society criteria for chronic bronchitis and emphysema participated in the study (10). These patients were mix cases involving chronic

* Presented at the 5th Marmara Medical Days, September 16-19, 1996 İstanbul

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Received: Nov 15, 1996 Accepted: Aug 14, 1997

bronchitis and emphysema together. 10 patients had severe and 5 patients had mild symptoms or signs of chronic airway obstruction especially according to FEV_1/FVC values. Nine of the patients were nonsmokers and six were heavy smokers (1-2 packet/day for 3 to 50 years). The patients who had coughing and mucus because of another pulmonary disease as tuberculosis, cancer, industrial pulmonary disease, the cases who were treated by antibiotics for a long period and taking another mucolytic agent were excluded. The COPD patients that were participated in the study were administered 600 mg/day (3x200mg) NAC ("Asist" Bilim İlaç San. ve Tic. Şti.) for 3 months and the platelet functions were evaluated before and after the therapy. In the control group there were 30 healthy people at the same ages. The patients and the control group didn't receive any agent that would effect the platelet functions during the study.

In the study, "Chrono-Log Whole Blood Lumi-Aggregometer (model 560, Chrono-Log Cooperation, Hoventoun P.A. U.S.A.) was used. In whole blood samples, platelet aggregation values were determined by electrical impedance method that was developed by Cardinal and Flower (11, 12 ,13,14,15). This method depends on the measurement of changing of electrical impedance between the platinum electrodes. The electrodes which are contacted with blood are surrounded by a layer of platelets. When the agonist agents are added, other platelets also accumulates and becomes sticky which causes an increase in impedance (16).

In the study, 500 ml venous blood sample and 500 ml saline were put in special siliconised cuvettes and aggregation responses which were given against ADP (10mM) and collagen (2ml/ml) were determined. Maximum aggregation rate (W/dk) was determined from highest point of the slope and maximum aggregation intensity (W) was determined from point of maximum impedance. Results were evaluated by Student's T test. Values of p below 0.05 were taken as significant. Linear correlation coefficient (r) was calculated for evaluating the relation between arterial oxygen tension (PaO_2) and haematocrit (Hct) values of the patients by correlation analysis.

RESULTS

Platelet aggregation responses (maximum rate and intensity of aggregation) to ADP and collagen of control group and COPD patients are presented in Table 1.

In COPD patients before NAC therapy ADP and collagen induced platelet aggregation rate and intensity were significantly higher with respect to the control group. After NAC therapy the maximum rate and intensity of collagen induced platelet aggregation decreased significantly but ADP induced platelet aggregation responses weren't changed (Table 1,2). Platelet aggregation values were similar in severe and mild cases. Before and after NAC therapy, relation between pO_2 and Hct values of the patients weren't found to be significant by correlation analysis (before: r=2113, after: r= 1803, p>0.05). (Figure 1)

DISCUSSION

In the presented study, in COPD patients it was observed that a) Platelets' aggregation responses to ADP and collagen were significantly higher than the healthy individuals. b) NAC therapy reduced aggregation rate and intensity significantly in collagen induced platelet aggregation.

Thus in COPD patients significant reduction of aggregation response to collagen by NAC treatment was determined by this particular study for the first time. This finding put forward an important evidence about reduction or prevention of hypercoagulability tendency and thromboembolism risk by oral NAC therapy (3x200) mg/day for 3 months in COPD patients in addition to its other beneficial effects.

In our study it was found that in COPD patients, NAC therapy decreased the platelet aggregation responses to collagen but didn't change it to ADP. Hogan

Table 1: Maximum rate and intensity of collagen and ADP induced platelet aggregation in control and COPD patients before NAC therapy.

		CONTROL	COPD (before NAC therapy)	P
Maximum aggregation rate (W/dk)	ADP	2.19±1.87	5.28±3.77	<0.01
	COLLAGEN	4.14±1.19	13.33±6.45	<0.001
Maximum aggregation intensity (W)	ADP	4.59±2.69	14.85±10.18	<0.001
	COLLAGEN	9.15±5.75	33.10±9.11	<0.001

Table 2: Maximum rate and intensity of collagen and ADP induced platelet aggregation in COPD patients before and after NAC therapy.

		COPD (before NAC therapy)	COPD (after NAC therapy)	P
Maximum aggregation rate (W/dk)	ADP	5.28±3.77	5.84±4.18	>0.05
	Collagen	13.33±6.45	8.73±4.70	<0.05
Maximum aggregation intensity (W)	ADP	14.85±10.18	12.14±10.42	>0.05
	Collagen	33.10±9.11	20.00±10.83	<0.01

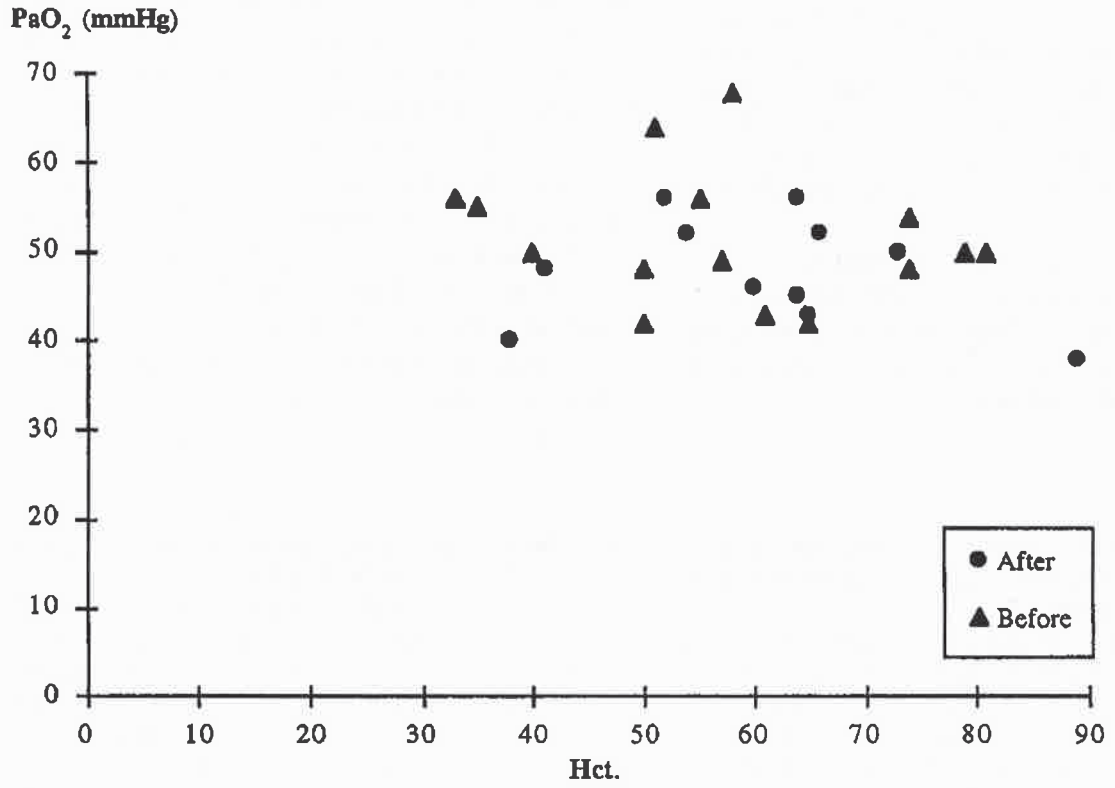

Fig. 1. Relationship between arteriel oxygen tension (PaO_2) and Heamatocrit (Hct) in the 10 patients studied before and after NAC therapy. (r = -2113, p>0.05 and r = -1803, p>0.05 respectively). Conversion: traditional units to SI: 7.5 mmHg = 1 kPa.

et al. also determined that in healthy individuals, co-administration of glyceryl trinitrate and NAC didn't change ADP induced platelets' aggregation responses (8). The induction mechanisms of platelet aggregation by ADP and collagen were quite different. The major effect of ADP on platelets is direct and specific fibrinogen binding sites appear on the platelet surface and dimeric fibrinogen molecule binds to two platelets. Whereas the effects of collagen depend on arachidonate metabolism to a considerable extent; arachidonic acid (AA) and its metabolites especially tromboxan A_2(TxA_2) mediates collagen induced platelets' aggregation response (17) .

It has been approved that increased production of free oxygen radical (FOR) from many sources mainly the infiltrated neutrophyles and/or insufficient antioxidant defense plays important role in the pathogenesis of COPD (1, 2, 3, 4, 5).

When the lungs are exposed to oxidants, lipid peroxidation reactions are induced by insufficiently detoxified (FOR), calcium homeostasis is disrupted, a_1-antitripsin (a_1-AT) is inactivated (18). It is known that inhibition of a_1-AT has important role especially in pulmonary emphysema pathogenesis. Thus Meloni et al. reported that, administration of a new thiol group compound P1507 [N-5 (thioxo-L-Prolyl) -L-Cysteine] prevented a_1AT inactivation by polimorf leucocyte

originated oxidants (19). Although the molecular mechanism hasn't been clear yet, one of the important FOR induced events is release of AA and production of TxA_2 (20). Therefore under the oxidative stress, the responsiveness of collagen induced platelets will increase. One of the important targets of oxidants are soluble and protein bounded sulfhydril groups. Sulfhydril containing compounds, especially reduced gluthatione (GSH) is important in protecting from peroxidative destruction of cells. GSH is transformed into oxidised glutathione (GSSG) during the glutathione peroxidase (GPX) catalysed metabolism of hydroperoxides. Under normal conditions GSSG is transformed into GSH rapidly but under the oxidative stress GSH decreases gradually, and concentration of GSSG inceases. Thus detoxification of hydroperoxides becomes insufficient (21).

In addition, GSSG may be reacted with protein sulfhydrill groups to produce protein-glutathione mixed disulfides (Protein S thiolation). It is suggested that S thiolation of many enzymes plays an important role in AA release and metabolism (20).

On the other hand, NAC is a thiol containing compound and shows its antioxidant effect by increasing plasma cysteine levels. Cysteine is a precursor of glutathione. Jankowska et al reported that, NAC protects lung cells aganist inhalated oxidants and/or oxidants that were produced by inflammatory leucocytes, by increasing intra and extracellular GHS in COPD patients. Oral NAC administration (3x200 mg/day) for 3 weeks decreased granulocyte activity and increased forced vital capacity (FVC) and forced expiratory volume (FEV_1) (22). Leuenbergen also suggested that, NAC therapy is an effective method for improving oxidant/antioxidant balance (9).

In conclusion, our findings showed that significantly increased aggregation response of collagen induced platelets was inhibited by NAC therapy in COPD patients and it was suggested that although the mechanism wasn't clearly explained yet, administration of NAC will be effective in preventing thromboembolic complications by regulating platelet functions in addition to its other therapeautic effects.

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SERUM SOLUBLE CD4 AND CD8 LEVELS IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS

Olcay Aydıntuğ* • Taşkın Şentürk* •Nurşen Düzgün*• Güner Tokgöz* • Hüseyin Tutkak*

SUMMARY

Several immunological abnormalities have been described in systemic lupus erythematos (SLE). The objectives of this study are to investigate the serum levels of soluble CD4 (sCD4) and soluble CD8 (sCD8) which an reflect in vivo T cell activation status and to assess whether sCD4 and sCD8 measurement can help in further characterization of the disease.

Forty patients with SLE and 20 apparently healhy controls were included in the study. All patients (35 females, 5 males) fulfilled the 1982 ARA criteria for the classification of SLE. The healthy controls consisted of 12 females and 8 males. Among SLE patients 20 had active and 209 had inactive disease. An ELISA (T Cell Diagnostics, Cambridge, MA) was used to measure the serum sCD4 and sCD8.

Although there was no statistically significant difference between mean sCD8 levels of patients with SLE and controls ($p>0.05$), serum mean sCD4 level in patients with active SLE was significantly increased as compared to that in the controls and in patients with inactive SLE ($p<0.05$ and $p<0.05$, respectively). High serum sCD4 levels correlated well with clinical disease activity, but there was no correlation between sCD4 or sCD8 levels and the laboratory parameters such as erythrocyte sedimentation rate, C-reactive protein, anti-ds DNA antibody, complement components 3 and 4 and immunoglobulins G, A and M.

We concluded that sCD4 may reflect clinical activity of the disease and allow an assessment of T cell activity

Key Words: *sCD4, sCD8, Systemic Lupus Erythematosus*

The CD4 and CD8 molecules are expressed on the surface of distinct populations of T lymphocytes. The CD8 molecule serves as a receptor for class I MHC and CD4 serves as a receptor for class II MHC molecules. Soluble forms of these molecules (sCD4 and sCD8) are prouced upon activation of corresponding lympocytes (1-4). The functional roles of these soluble molecules are not very clear. Cell surface molecules can be shed by activated T lympocytes and measured in serum to assess in vivo T cell activation (5). Increased serum sCD4 and/ or sCD8 have been reported in some viral infections and several diseases in which immunological mechanisms have been implicated in the pathogenesis (6-14). Soluble CD_ molecule release is reported to occur by alternative splicing of mRNA resulting in a secretory protein lacking a transmembrane domain (15,16). The mechanism of CD4 release is not yet clear but it is likely that release occurs through proteolytic cleavage at the cell surface.

SLE is an autoimmune disorder characterized by a variety of immunologic abnormalities. These abnormalities are presumably due to some aberration of immunocompetent cells abnormalities as represented by a decreased response to various mitogens (17), B cell abnormalities such as polyclonal B cell acivation (18), an impaired autologous mixed lymphocyte reaction (19), monocyte dysfunction (20) and an impaired production of lympokines (21).

The aim of thes study is to measure serum sCD4 and sCD8 levels in active and inactive SLE patients, to compare the results with those of healthy controls and to search for a relationship with clinical and laboratory markers of disease activity.

PATIENTS AND METHODS

Forty patients with SLE and 20 apparently healthy controls were included in the study. All patients fulfilled the American Rheumatism Association (ARA) 1982 Revised Criteria for the Classification of SLE (22).

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Received: June 23, 1997 Accepted: July 17, 1997

Table 1: Serum sCD4 and sCD8 levels in patients with SLE and healthy controls

	sCD4 (mean±SD U/ml)	sCD8 (mean±SDU/ml)
Healthy controls (n=20)	(10.9±3.3)	(226.3±90.4)
Active SLE (n=20)	(17.4±15.9) ***a,b***	(285.2±178.8) ***c,d***
Inactive SLE (n=20)	(9.5±3.3) ***a***	(256.6±138.2) ***a***

a: p<0.05 when compared with healthy controls.
b: p<0.05 when compared with inactive SLE
c: p> 0.05 when compared with healthy controls.
d: p>0.05 when compared with inactive SLE.

The patients with SLE consisted of 35 females and 5 males (mean age ± SD, 33.2 ± 11.2 years, range 16-60). The healthy controls consisted of 12 females and 8 males (mean age 32.2 ± 9.6 years, range 21-49). Among the patients with SLE, 20 had active disease (16 females and 4 males mean age 33.1 ± 10.9 years, range 16-54) and 20 had inactive (19 females and one male, mean age 33.3 ± 11.7 years, range 19-60). Disease activity of SLE patients was defined according to the SLE Disease Activity Index (SLE-DAI) criteria (23).

Eighteen patients with active SLE were on high dose corticosteroid therapy (60-80 mg/day). Among these patients two ere also taking oral cyclophosphamide (150 mg/day), 2 patients were on chloroquine (250 mg/day). One patients was on cyclosporin-A (200 mg/day), 6 were on chloroquine (250 mg/day), 2 were on oral cyclophosphamide (100 mg/day) and 2 patients were not receiving any medication.

Serum sCD4 and sCD8 concentrations were determined by a sandwich ELISA (T Cell Diagnostics, Cambridge, MA) in sera which had been stored at -20°C until use. The procedures suggested by the manufacturer were follojwed without any modification and the optical absorbanca values were read on an ELISA reader at a wavelength of 490 nm. All samples were tested in duplicate and sCD4 and sCD8 levels were calculated by comparing the mean absorbanca of duplicatesamples with that of the standard curve. Serum sCD4 and sCD8 levels are given as U/ml (one unit is defined by the manufacturer as the amount of CD4 and CD8 found in 103 Jurkat T cells lysed with 1% NP40). The mean sCD4 value of normal human sera determined by this kit is given as 8.1 U/ml (range 0-18 U/ml) with a kit sensitivity of 1.1 U/ml.

The mean sCD8 value of normal human sera determined by this kit is given as 336 U/ml (range 138-533 U/ml) with a kit sensitivity of 50 U/ml.

Erythrocyte sedimentation rate (ESR) was determined by Westergren method. Serum levels of C-reactive protein (CRP), complement component 3 (C3c), complement component 4 (C4), immunoglobulin G (IgG), immunoglobulin A (IgA) and immunoglobulin M (IgM) were measured by nephelometry (Behring). Anti-ds DNA antibody was measuredby radioimmunoassay (Amersham).

Statistical analyses were performed by student T test, Mann-Whitney U test and correlation analysis.

RESULTS

Serum mean sCD8 level in active SLE patients (295.2±178.8 U/ml, mean±sD) was not significantly different than that in the inactive SLE patients (256.6±138.2) and normal controls (226.3±90.4) (p>0.05, respectively). The amount of serum sCD4 in the patients with active SLE was significantly increased as compared to that in the controls (17.4±15.9 vs 9.5±3.3, p<0.05) (Table 1).

Serum levels of ESR, CRP, anti-ds DNA, C3 and C4 in patients with active SLE were significantly different than in the inactive patients with SLE (p<0.001). There was no statistically significant difference between IgG, IgA and IgM levels of active and inactive SLE patients. (p>0.05) (Table 2). Serum sCD4 and sCD8 levels did not correlate with the laboratory parameters such as anti-ds DNA antibody, C3c, C4, IgG, IgA and IgM, ESR and CRP (p>0.05). No clinical or laboratory features distinguished the patients with markedly elevated sCD4 levels.

DISCUSSION

To the best of our knowledge, studies on the levels of sCD4 and sCD8 in SLE are scarce. Sawada et al. (24) have found that sCD4 and sCD8 levels were higher in patients with active and inactive SLE as compared to healthy controls. They have observed a posi-

Table 2: Various laboratory prameters in patients with SLE.

	Active SLE (mean±SD)	Inactive SLE (mean±SD)	p
Anti-ds DNA (IU/ml)	103.9±93.3	41.4±52.9	p<0.05
Complement 3 c (mg/dl)	0.58±0.33	0.64±0.21	p<0.05
Complement 4 (mg/dl)	0.16±0.12	0.23±0.25	p<0.05
IgG (g/L)	21.9+6.2	17.7±6.8	p>0.05
IgA (g/L)	3.5±1.8	2.8±1.4	p>0.05
IgM (g/L)	1.9±1.0	2.4±1.6	p>0.05
CRP (mg/dl)	24.7±36.7	3.3±2.0	p<0.05
ESR (mm/hour)	76.2±30.9	18.5±8.2	p<0.05

tive correlation between serum sCD4 and the anti-DNA, a negative correlation between serum sCD4 and C3, and a positive correlation between serum sCD8 and ESR levels. In our study, the serum mean sCD4 level was significantly increased in patients with active SLE as compared to that in the inactive patients and controls ($p<0.05$) which was in harmony with Sawada's results, but serum mean sCD8 level was not statistically different than the levels found in inactive SLE and control subjects ($p>0.05$). Moreover, we did not determine a significant correlation between these molecules and various laboratory parameters such as anti-ds DNA, C3c, C43, IgG, IgA, IgM, CRP and ESR ($p>0.05$).

Immunophenotyping and immunohistology of T cell subsets can give valuable information about the numbers and distribution in pathological tissues but they do not provide functional information about the correspondings subsets. Suggesting a clear relationship between sCD4, sCD8 levels and the state of in vivo T cell activation is not very simple due to natural fluctuations and the possible impact of various therapies. In the present study we did not investigate the number of CD4 and cD8 positive cells. Our study is a cross-sectional work and we did not investigate the numbers of CD4 and CD8 positive cells. Our study is a cross-sectional work and we did not make prospective sequential studies of individual patients. Various drugs taken by our patients might have influenced our results. The significance of any changes in the levels of these soluble molecules can be rather speculative as their levels have been reported to change in several viral diseases (8,9,25,26). At present little is known about the kinetics and magnitude of soluble molecule release after in vivo activation, the clearence of these molecules from the circulation and the influence of therapy and disease activity (27).

The biological and immunological functions of the sCD4 and sCD8 molecules are not yet well understood. sCD4 and sCD8 molecules have been demonstrated to retain the ability to bind to their corresponding MHC molecules (28,29). These soluble molecules may stimulate or inhibit the interaction of CD8 T cells with their target cells and CD4 T cells with APCs leading to aberration of CD8 or CD4 T cell activation or function. However, it is shown in vitro that recombinant sCD4 protein connot inhibit class II-specific T cell interactions (30). This suggests that sCD4 is not likely to be an immunoregulatory molecule. If sCD8 retains the ability to bind to class I MHC molecules, it may inhibit the interaction of CD8+ T cells with their antigen bearing cells leading to a own regulation of CD8+ T cell activation or funciton (26).

The class II MHC antigen is believed to act in signal transduction in B cell activation (31) and to promote differentiation to the antibod secreting cells (32). Therefore, an increased sCD4 level observed in active SLE patients might also be responsible for the activation of B cells, stimulating immunoglobulin production, so leading to hypergammaglobulinemia. However we did not determine a positive correlation between sCD4 and anti-ds DNA or immunoglobulin levels.

In conclusion, this study showed that in patients with active SLE, serum levels of sCD4 but not sCD8 were increased. This may reflect an immune activation state of CD4+ T lymphocytes, and increased levels of sCD4 levels might be responsible for the activation of B cell and hypergammaglobulinemia in SLE. Serum sCD4 and/ or sCD8 measurement can help to assess the in vivo immune system activation in several inflammatory and immunological diseases along with a potential to provide new insights to the immunopathogenesis of such disorders.

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COMPARISON OF THE EFFICACY OF SUBCUTANEOUS AND SUBLINGUAL IMMUNOTHERAPY IN MITE SENSITIVE PATIENTS WITH RHINITIS AND ASTHMA-A PLACEBO CONTROLLED STUDY

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SUMMARY

Thirty-six patients with rhinitis and asthma due to mite allergy were randomly divided into 3 groups in order to receive; subcutaneous injections with calcium phosphate extracts, sublingual drops with solutions of purified standardized allergen preparation(Stallergenes) or placebo for a period of one year. Assessment of clinical and immunological efficacy was done according to; symptom and medication scores, methacholine provocation tests, skin prick tests, Dermatophagoides pteronyssinus(D. pteronyssinus) and Dermatophagoides farinae(D. farinae) specific IgE and IgG4 concentrations. The clinical outcome of subcutaneous immunotherapy(SCIT) for both rhinitis and asthma was satisfactory. Patients treated with sublingual immunotherapy(SLIT) had decreased rhinitis symptoms ($p<0.01$) but no change in asthma scores($p>0.05$). Total drug consumption significantly decreased in both actively treated groups($p<0.01$) at the first year compared with baseline. When skin prick tests were evaluated; subcutaneously treated group had a significant decrease in the wheal diameter of D. pteronyssinus ($p<0.01$), D. farinae($p<0.05$) and histamine($p<0.05$), while other two groups showed no difference ($p>0.05$). There was no significant change in methacholine PC20 values in all groups at the end of the first year when compared with baseline($p> 0.05$). From the serologic point of view, no change in D. pteronyssinus and D. farinae specific IgE levels were observed, however specific IgG4 concentrations were significantly higher than baseline both in SLIT and SCIT groups($p<0.05$) after one year immunotherapy. No significant difference was obtained in any of these parameters in the placebo group ($p>0.05$). In conclusion; our data allow us to give a positive judgment on SLIT, especially in patients with allergic rhinitis. Furthermore, we believe that sublingual immunotherapy has to be taken into account in the therapy of allergic asthmatic patients with the consideration of its safety and economical aspects. However; before having a final decision on SLIT, it seems necessary to follow up the patients for longer periods and to see whether clinical efficacy lasts even after immunotherapy ceased.

Key Words: *Sublingual immunotherapy, Allergic rhintis, Asthma, Mite sensitivity*

Specific immunotherapy with extracts of inhalant allergens has been reported to be effective in ameliorating clinical symptoms of respiratory allergic diseases. However there is still controversy concerning the underlining mechanisms by which it works.

A classical schedule with subcutaneous injections of allergen can be associated with local, systemic reactions and even anaphylactic death has been reported following allergen injections (6,22,23). Therefore, new administration routes have been proposed to overcome the disadvantages of subcutaneous immunotherapy. Oral mucosa like nasal mucosa is known to be a potentially useful site for the absorption of both drugs and allergens. For this reason sublingual administration of soluble allergen extracts has currently been under test, both positive and disappointing results have been reported, but generally, the procedure has been shown to be efficacious (18).

The aim of this prospective, placebo controlled, parallel group study was; to evaluate the clinical and immunological outcome of two forms of immunotherapy- subcutaneous and sublingual- and to compare the results with placebo in 36 patients with rhinitis and asthma due to mite allergy.

MATERIALS AND METHODS

Patient selection:

Thirty-six patients (7 males and 29 females, mean age: 31.33 years, range 18-46 years) were included into the study. Diagnosis of rhinitis was made according to the "International Consensus Report on the Diagnosis and Management of Rhinitis" criteria (12). The diagnosis of asthma was made by clinical history and laboratory documentation of reversible airway obstruction (1,13).

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Received: June 9, 1997 Accepted: July 17, 1997

Inclusion criteria were as follows:

1. A clinical history of hypersensitivity to inhaled house dust mites with symptoms of rhinitis and asthma for at least three consecutive years.
2. Presence of symptoms despite optimal treatment and environmental controlling procedures.
3. FEV1 greater than 70% of predicted.
4. A positive skin test to extracts of *D. pteronyssinus* and *D. farinae*
5. A positive in vitro specific IgE test to *D. pteronyssinus* and *D. farinae*
6. No hypersensitivity to any other allergen except house dust mites.
7. No immunotherapy with any extract before.

Other exclusion criteria were active immunologic and systemic diseases as well as malignancy of any system. All patients gave informed consent before admission to the trial and the study received approval from the university ethics committee.

Study design:

Patients were separated into three groups ; SLIT (n= 15), SCIT (n=10) and placebo (n=11).

Patients were asked to record daily symptom scores in diary cards according to the scale described by Tari et al. all through the study (25). All patients except three were receiving inhaled corticosteroids at the beginning of the study. Every 3 months, a physician evaluated the patients in order to reduce the inhaled corticosteroid dose and quit if it was possible. Salbutamol for asthmatic complaints and H1 antagonists for rhinitis symptoms were the only rescue medication allowed. The patients were instructed to use these drugs when needed and to record the amount of rescue medication in the diary cards. Mean monthly medication scores were calculated according to the scale shown in table 1. The mean basal symptom and medication scores were compared with the mean of the first and second six months of therapy.

At the start and at the end of the first year; skin prick tests and bronchial challenge with methacholine were performed. Total, specific IgE and IgG4 were assessed at the beginning, 6th and 12th months of study.

Skin prick tests:

SPTs were performed with a standardized panel (Stallergenes , France) of airborne allergens including ; grass, tree and weed pollens, molds, *D. pteronyssinus, D. farinae,* cat and dog dander. A wheal size greater than 3 mm was evaluated as a positive result.

Bronchial challenge test:

Methacholine inhalation test to determine airway responsiveness was performed with the method described by Cockroft et al.(7).

Table 1. Medication scores

Medication	Score
No drug	
Corticosteroids	
400 micrograms/day	1
400-800 micrograms/day	2
800-1500 micrograms/day	3
over 1500 micrograms/day	4
β2 agonist	
less than 2 times a week	1
2 times a week or more	2
everyday	3
long duration β2 agonist	4
Antihistamine	
less than 2 times a week	1
2 times a week or more	2
every day	3
nasal steroids	4

Serum total and specific IgE and IgG4 were analyzed by Pharmacia CAP system according to the manufacturer 's instructions.

Treatment schedules:

In SLIT protocol drops of *D. pteronyssinus* + *D. farinae* extract or placebo were used (Stallergenes, France). Progression of doses was made in 65 days. It started with 1 drop of 0.1 IR/ml up to 15 drops on day 15, while on days 15-30, 1-15 drops of 1 IR/ml; on days 30-45, 1-15 drops of 10 IR/ml were given. Finally, from days 45-65 patients received 1-20 drops of 100 IR/ml. Once this dose was reached, maintenance treatment continued with 100 IR/ml vial ; 20 drops every day for one month and than 20 drops two days a week.Placebo drops in the same glycerol saline diluent were administered in the same way as sublingual extracts. The drops were taken sublingually in the morning before breakfast and were kept in the mouth for at least 3 minutes. To allow for maximum absorption, subjects were instructed not to eat or drink for 15 minutes.

In SCIT protocol calcium phosphate extracts from Stallergenes, France were used. The initial concentration was 0.1 IR/ml of *D. pteronyssinus* and *D. farinae* extract, followed with 1 and 10 IR/ml concentrations, the doses were increased at weekly intervals until maximum tolerated dose was achieved (varying from 0.15 to 0.75 ml) and continued at 2 week intervals for 3-6 months and than 4 week intervals.

Statistics:

In the evaluation of symptom and medication scores and skin test data; Kruskal Wallis H test was

used to determine the difference between all groups, when significance was indicated the two sample Mann Whitney U test was applied. Within group differences in certain time intervals were analyzed by Friedman two way Anova test for the determination of global difference and by Wilcoxon's signed rank test when significance was observed. Inter and within group differences in specific IgE and IgG4 data were analyzed by repeated measurements Anova. In the evaluation of total IgE and provocation test data geometric means were used.

RESULTS

All patients (15 SLIT, 11 placebo, 10 SCIT) completed the study. The three groups were comparable concerning age, sex and duration of symptoms (Table 2).

Individual symptom and medication scores of all 3 groups are given in Tables 3,4 and 5. Mean symptom scores for rhinitis decreased significantly in the first ($p<0.01$) and second six months(SLIT: $p<0.01$, SCIT: $p<0.05$) of therapy when compared with baseline both in SLIT and SCIT groups. When asthma scores were evaluated SCIT group had higher basal scores than SLIT group($p=0.049$). Mean asthma symptom scores decreased significantly in the first and second six months of therapy when compared with basal scores in the SCIT group ($p<0.01$). Although there was a decline in mean asthma scores throughout the study, no significant difference between time intervals was

Table 2. Charasteristics of patients

	SLIT	SCIT	PLACEBO
Number of subjects	15	10	11
Male/female	2/13	4/6	1)10
Mean age (years)±SD	31.67±7.28	28.70±6.57	33.27±8.45
Age distrubiiton (years)	18-41	18-39	18-46
Mean duration of disease (years)	5.67±4b32	6.20±2.97	7.27±3.07
Basal drug consumption (number of patients)			
İnhaled steroids	13	10	10
antihistamins	15	10	11
β2 agonists	13	10	11
* Total IgE (kU/L)	505.05	311.89	288.40

* Total IgE values are given as geometric means.

Table 3. Individual asthma, rhinitis and total medication scores in SLIT group

	Asthma Scores			Rhinitis Scores			Total Medication		
Patients	*0	*1	*2	0	1	2	0	1	2
1	1.5	1.1	0.7	1.3	1.0	0.7	4.0	3.7	1.5
2	0.5	0.6	0.1	0.9	0.6	1.5	6.0	4.8	3.7
3	0.7	0.2	0.2	0.9	0.5	0.5	5.0	2.5	0.2
4	1.2	0.7	0.2	0.9	0.4	0.2	7.0	6.2	3.5
5	0.5	0.2	0.2	0.4	0.2	0.2	7.0	3.2	2.5
6	0.1	0.0	0.0	0.4	0.3	0.1	2.0	0.8	0.2
7	0.0	0.1	0.1	0.8	0.3	0.1	4.0	3.3	2.3
8	1.5	0.8	1.3	1.7	1.1	1.4	6.0	3.7	2.7
9	0.6	0.9	0.3	0.9	1.1	0.5	4.0	3.2	0.8
10	0.1	0.2	0.1	0.5	0.3	0.1	3.0	1	0.3
11	0.6	0.7	0.6	0.6	0.7	0.7	6	4.5	0.5
12	0.3	0.4	1.1	0.1	0.1	0.1	10	7.7	3.5
13	0.9	0.9	0.5	1.3	1.4	0.6	4	3.7	1.6
14	0.0	0.3	0.1	2.1	1.6	0.6	4	3.3	2
15	1.0	0.5	0.7	0.3	0.2	0.2	2	1.3	4.3

*0 baseline (mean of 1 month before therapy)
*1 mean of the first 6 months of therapy
*2 mean of the second 6 months of therapy

Table 4. Individual asthma, rhinitis and total medication scores in SCIT group

	Asthma Scores			Rhinitis Scores			Total Medication		
Patients	*0	*1	*2	0	1	2	0	1	2
1	2.4	1.7	1.8	1.8	1.4	1.5	7.0	6.3	6.2
2	1.0	0.5	0.7	0.4	0.5	0.7	6.0	4.4	5.6
3	1.2	0.1	0.3	0.1	0.0	0.0	10.0	8.4	8.3
4	0.9	0.2	0.1	0.3	0.1	0.1	4.0	3.6	1.2
5	0.7	0.6	0.2	0.4	0.1	0.1	6.0	5.8	3
6	1.8	1.4	1.1	1.0	0.3	0.3	7.0	6.7	3.7
7	0.5	0.1	0.4	0.9	0.9	0.9	8.0	4.5	2.5
8	0.9	0.6	1.0	1.4	0.7	0.7	4.0	2.3	2.3
9	0.9	0.5	0.2	0.0	0.0	0.0	5.0	4.8	2.2
10	1.8	1.2	0.1	2.1	0.2	0.2	11.0	7.2	4

*0 baseline (mean of 1 month before therapy)
*1 mean of the first 6 months of therapy
*2 mean of the second 6 months of therapy

Table 5. Individual asthma, rhinitis and total medication scores in placebo group

	Asthma Scores			Rhinitis Scores			Total Medication		
Patients	*0	*1	*2	0	1	2	0	1	2
1	0.1	0.3	0.3	0.4	0.6	1.1	6	5.5	3.3
2	0.2	0.3	0.3	1.0	0.8	1.0	4	4.7	3.2
3	1.3	2.2	2.0	1.3	2.1	2.0	11	8.5	6.5
4	0.8	0.6	0.5	0.8	0.5	0.5	4	4.7	3.8
5	0.7	1.1	2.5	0.0	0.0	0.2	8	5.8	7.5
6	0.1	0.2	0.2	0.9	0.7	0.4	7	6.8	5.7
7	1.7	1.1	1.4	0.4	0.3	0.2	5	5	6
8	0.6	1.2	1.2	1.2	0.9	0.4	5	3.3	5
9	0.2	0.2	0.0	1.1	1.0	0.3	2	4.3	3.3
10	1.5	1.5	1.2	1.3	1.2	1.2	9	9	7.3
11	0.6	0.2	0.1	0.6	0.3	0.1	6	6.3	6

*0 baseline (mean of 1 month before therapy)
*1 mean of the first 6 months of therapy
*2 mean of the second 6 months of therapy

observed in the SLIT group($p > 0.05$).Placebo group had no significant change in mean rhinitis and asthma scores all over the study ($p>0.05$) (figure 1:A,B).

Mean total medication scores decreased significantly in the first (SLIT: $p<0.001$, SCIT: $p< 0.01$)and second periods ($p<0.01$) of immunotherapy when compared with baseline both in SLIT and SCIT groups (figure 1:C). Total medication scores had no significant change throughout the study in the placebo group ($p>0.05$).

Skin sensitivity to *D. pteronyssinus*, *D. farinae* and histamine diminished significantly at the 12th month of immunotherapy in SCIT group when compared with basal measurements ($p<0.01$, $p<0.05$, $p<0.05$, respectively). No significant change between the beginning and the end of therapy was found in the SLIT and placebo group for the same antigens and histamine ($p> 0.05$).

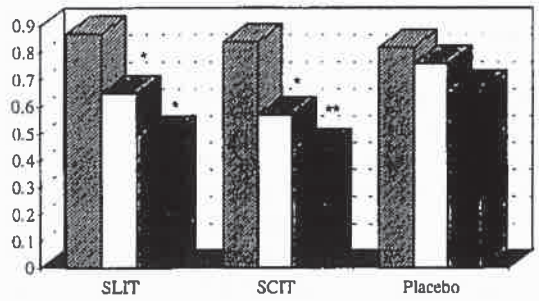
From a serologic point of view, no change in *D. pteronyssinus* and *D. farinae* specific IgE were observed in the 6th and 12th months of therapy compared with baseline in either the actively treated or the placebo groups. Also no intergroup differences were seen ($p> 0.05$).

When specific IgG4 levels were evaluated; in SLIT group 12th month IgG4 concentrations increased significantly when compared with baseline, whereas in the SCIT group both 6th and 12th month measurements were higher than basal values ($p<0.05$). Intergroup differences were only significant in the 6th and 12th months, the mean IgG4 levels of SCIT group in these time intervals were higher than SLIT and placebo($p<0.05$) (figure 2).

Methacholine bronchial provocation tests showed no significant differences at the first year of the trial when compared with basal values in all three groups ($p>0.05$).

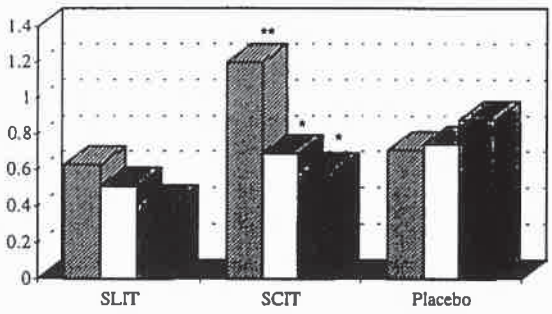
Cumulative doses achieved at the end of the first year were 11316 IR and 131 IR for SLIT and SCIT groups, respectively.

A



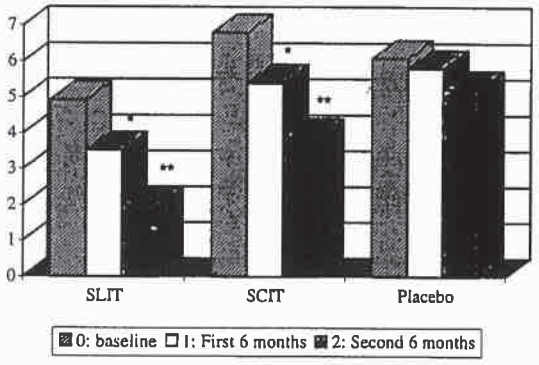
* Lower than baseline (p<0.01), ** lower than baseline (p<0.05)

B



* Lower than baseline (p<0.01), ** higher than SLIT baseline (p=0.49)

C



* Lower than baseline (SLIT: p<0.001, SCIT: p<0.01)
** lower than baseline and first 6 months (SLIT: p<0.001, p<0.01, SCIT: p<0.01, p<0.05, respectively)

Fig. 1. A. Rhinitis Scores
B. Asthma Scores
C. Total Medication Scores

In the SCIT group there were few side effects all in the induction phase, as; local reactions larger than 5 centimeters in two patients, mild bronchospasm in one patient. The side effects seen in SLIT were negligible; buccal pruritis in one and nausea in an other patient which all disappeared after reduction in the allergen dose.

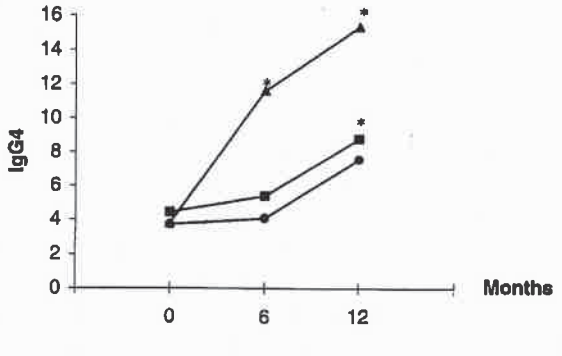
DISCUSSION

Although the clinical efficacy of allergen specific immunotherapy has been established by a number of controlled trials (14,15,20), it nonetheless may be associated with local, general and even fetal reactions(6,22,23). In the search for efficacious forms of immunotherapy with less side effects, compared with classical subcutaneous immunotherapy, some alternative forms used during the first decades of this century were recently reintroduced. The aim of this study was; to evaluate the clinical and immunological outcome of two forms of immunotherapy- subcutaneous and sublingual- and to compare the results with placebo in 36 patients with rhinitis and asthma due to mite allergy.

The clinical outcome of subcutaneous immunotherapy in our patients was satisfactory. Both rhinitis and asthma symptom scores improved significantly, there was a significant reduction in antihistaminic and inhaled corticosteroid consumption and the therapy was well tolerated.

Sublingual administration of soluble allergen extracts is currently under test, however its routine use in

A



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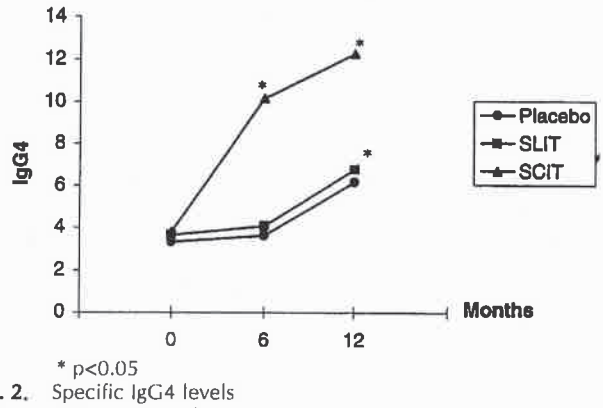

* p<0.05

Fig. 2. Specific IgG4 levels
A) D. pteronyssinus
B) D. farinea

clinical practice is still the object of controversy. Both positive(8,21,24,25,26) and disappointing(17,19) results have been reported but generally, the procedure has shown to be efficacious. In the vast majority of studies pollen extracts have been used via the sublingual route(8,21,26). There are few studies concerning the efficacy of SLIT with mite extracts. Tari et al, assessed the efficacy of SLIT in patients under 12 years of age who were positive to mites. A significant reduction of nasal and respiratory symptom scores was already observed after 12 months of treatment and it became even greater after 18 months. The same significant difference between groups was also shown in medicine consumption(24,25). However, in another study, Piazza and coworkers reported that, subcutaneous but not sublingual and local nasal immunotherapy induced a significant clinical benefit in mite sensitive patients with chronic rhinitis(19). In our SLIT group, there was a significant clinical benefit in rhinitis symptoms. Although not at significant level, asthma scores decreased throughout the trial, furthermore b2 agonist and inhaled corticosteroid consumption was lower at the second part of the therapy. However placebo group failed to have a reduction in drug consumption. This means that sublingually treated patients consumed less drugs than the placebo group for similar symptoms.

There is conflicting data about the influence of immunotherapy on nonspecific hyperresponsiveness in asthma(5). In house dust mite asthma some authors have demonstrated an improvement(10) whereas others demonstrated even an increase(16) in nonspecific hyperresponsiveness after immunotherapy. In the case of mite sensitivity, it appears more difficult to influence hyperresponsiveness with immunotherapy, when allergic patients are continuously exposed to antigen in an uncontrolled manner. It is reported that only prolonged immunotherapy could possess a modulatory activity on the degree of bronchial inflammation(9). In line with the majority of investigations, neither the actively treated nor the placebo groups had significant improvement in bronchial hyperreactivity at the first year in our study.

It is reported that the immediate and late phase skin responses to allergen are reduced after immunotherapy, however the exact mechanism of this effect is not certain(15,27). Clinical improvement in the subcutaneous treated group in our study was accompanied by decreased skin sensitivity to *D. pteronyssinus* and *D. farinae* extracts and histamine. Although there were favorable clinical results in our SLIT group, no significant variations in cutaneous sensitivity was observed.

From the serologic point of view, *D. pteronyssinus* and *D. farinae* specific IgE levels didn't show significant modifications at the 6th and 12th months of our trial in comparison with baseline in either group as it is usually found in most immunotherapy procedures(3), whereas specific IgG4 concentrations in the actively treated groups showed a significant increase from basal levels. Recent data suggest that assessment of clinical effectiveness of immunotherapy is particularly based on clinical findings (14,15)and it is reported that increase in serum IgG levels do not correlate with the clinical benefit from immunotherapy(4). The clinical effectiveness of sublingual administration of allergens associated with a significant increase in serum specific IgG4 antibodies were reported in few controlled trials (24,26), on the contrary some investigators found no significant difference in IgG4 antibodies in their sublingual immunotherapy courses (8,17,19).In our subcutaneously treated group clinical benefit was supported by a significant increase in IgG4 antibodies even at the 6th and 12th months of immunotherapy. Although not so striking, sublingually treated patients had favorable clinical results besides increased IgG4 levels at the first year of therapy. These clinical and immunological data obtained in our study brings up the question that, if IgG4 antibody is an allergen blocking antibody and whether IgG4 assays can be used to monitor immunotherapy. Although many investigations lack to show a correlation between IgG4 antibody titers and decrease in symptom scores, exceptions can be found on an individual patient basis(2). The favorable clinical results were supported with an increase in IgG4 blocking antibodies in the subcutaneously and to a lesser extent sublingually treated groups in this study.

The slight difference in clinical and immunological benefit from immunotherapy in this study brings up the hypothesis that oral immunotherapy may work through different mechanisms from subcutaneous therapy, although it is suggested to be clearly able to effect the immune system. The mechanisms by which SLIT works is largely unknown but there are a number of possible explanations. It is suggested that allergen exposure of the oral mucosa is capable of modifying allergic reactivity, independent of events that may follow swallowing of the allergen (25). The precise mechanism remains to be defined, however it is reported to involve stimulation of allergen specific suppresser cells in the regional lymph nodes draining the oral mucosa, with less effect on serum antibodies(26).

On the other hand, one of the problems about oral and sublingual immunotherapy is the loss of allergenic activity due to digestive process in the mouth and stomach (18). This brings the discussion that whether peptides coming from the degradation of the extract could induce appropriate immune response and what should be the total dose administered. Using

a grass pollen oral and sublingual immunotherapy extract, Igea and coworkers observed a 3.8 fold loss of allergenic activity after a 30 second incubation with saliva, 10.3 fold loss after a subsequent 5 minutes incubation with gastric fluid. The authors suggest that, even with sublingual administration, extracts could undergo an evident loss of activity that should be taken into account when considering the total dose to be administered (11). In our study, the cumulative dose reached by SLIT at the end of the first year was about 80 times greater than the cumulative dose achieved by subcutaneous route. The more favorable results obtained by subcutaneous immunotherapy in comparison with sublingual route in this study, might be explained by this loss of allergenic activity and inadequacy of the total dose hypothesis.

A very substantial advantage shown by the sublingual route over the conventional route is the lack of serious side effects. In our study, sublingual treatment proved to be safe and only negligible side effects were observed. This method seems to be particularly economical not only for medical care but also because of loss of working time which is frequent in injection desensitization. It is reported that alternative routes allow social savings that has to be added to the favorable risk/benefit ratio (18).

In conclusion; we observed satisfactory data in subcutaneous immunotherapy for both rhinitis and asthma on the clinical and immunological basis. Furthermore; with sublingual immunotherapy clinical data for rhinitis was favorable; from the respiratory point, drug consumption was lesser with a decline in asthmatic scores throughout the trial. In the light of these data, with the consideration of its safety and economical aspects, sublingual immunotherapy has to be taken into account in the therapy of an allergic asthmatic patient. However, we believe that more conclusive data are required about the duration of clinical benefit after cessation of therapy before having a final decision. The clinical usefulness of sublingual immunotherapy when administered for a longer time and the mechanisms underlying its immunological effect also deserve additional studies both at the clinical and experimental level.

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THE RESULT OF GASTROCYSTOPLASTY IN RAT MODEL

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Ünsal Han** • Sedat Ünal*

SUMMARY

In the presented study, gastrocystoplasty in rats and related biochemical, physiological and histopathological results are discussed. 30 rats were grouped as follows: Control and Sham (Group A), animals with gastrocystoplasty (Group B). Urine pH, blood pH and bicarbonate levels, bladder capacity and end filling pressures were evaluated in all groups. After the gastrocystoplasty, group B showed a statistically significant increase in bladder capacity. Aciduria developed in 34 percent of rats in group B. In group A aciduria wasn't noted. No statistically significant difference was observed in blood pH and bicarbonate levels and end-filling pressure measurements in each group of rats. Significant histopathologic changes of the bladder occurred in the gastrocystoplasty group. In the 15 bladders examined histologically in group B, 2 had a papilloma on the mucosal surface of the transplanted gastric patch. The bladder mucosa adjacent to the transplanted gastric patch had pronounced hyperplastic and squamous metaplastic changes. Possible etiologies and differences of gastrocystoplasty related pathologic changes between two groups are discussed.

Key Words: *Gastrocystoplasty, Bladder Augmentation*

A patch obtained from the greater curvature of the stomach has been used for augmentation of poorly compliant bladder (1). Also, gastrocystoplasty has been reported to be a useful alternative to intestinal segment bladder enhancement in patients with compromised renal function (2). The advantages of using the stomach include protection against hyperchloremic acidosis, reduced mucus production and decreased urine infection rates (1,2,3). Asiduria is a known complication of gastric cystoplasties (4,5,6). On the other hand the histopathological changes that lead to malignancy have been noted in the transplanted gastric tissue and in the adjacent bladder wall in rats (7,8,9).

In the presented study, we investigated the effects of gastrocystoplasty.

MATERIALS AND METHODS

The experiment was performed in 30 male Sprague-Dawley rats weighing 235-280 grams. The animals were divided 3 groups: group A- 5 rats that underwent sham operations and 5 rats served as nonoperated controls, group B-20 rats that underwent gastrocystoplasty. All the animals were operated under ketamine anesthesia with a full-midline incision. In group B wedge (Mitchell) gastrocystoplasty was performed on 20 rats as follows: The gastroepiploic vessels were divided along the stomach. When the gastric wedge is taken the decision has to be made as to which right gastroepiploic artery will be preserved as a pedicle for the gastric flap. The gastric wedge is outlined with a marker pen with the apex near but not including the lesser curvature. The length of the wedge along the greater curvature was 15 mm. The bladder was bivalved by a generous midline incision. A full thickness anastomosis of stomach to bladder was completed with a single layer interrupted sutures using 6/0 vicryl. The opening in the stomach was closed in two layers using 5/0 silk sutures.. The sham group underwent laparotomy, cystotomy and closure with the same suture material. In all the groups the abdominal wall and skin were closed with 4/0 silk sutures. Postoperativelly sulfomethaxosale-trimethoprim suspension was added to drinking water of the animals for the first week.

Preoperativelly urine pH, bladder capacity and end-filling pressures were measured in each group of animals. 22 gauge intracath was punctured into the

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Received: Jan 6, 1997 Accepted: July 17, 1997

Table 1. Bladder capacity and end-filling pressure values pre and postop in each group of rat

	Bladder Capacity (ml)		*End-Filling Pressure* (cm/H2O)	
	Preop	Postop	Preop	Postop
Group A				
Control	2,67±0,24	-	23,25±3,65	-
Sham	2,18±0,36	2,07±0.44	23,40±1,76	25,46±2,53
Groub B				
(Gastrocystoplasty)	2,65±0,24	4,23±0,64	23,43±1,61	22,04±3,76

NOTE. Data are expressed as mean ±SD. The Student's t test was used for statistical analysis.
*P<.001 compared with group A

Table 2. Blood pH and bicarbonate levels and aciduria percent of each group of rats

	Blood pH	*Blood HCO3-*	*Aciduria* (%)	*Hematuria* (%)
Group A				
Control	7,37±0,15	26,45±0,93	-	
Sham	7,36±0,24	26,44±0.87	-	11
Groub B				
(Gastrocystoplasty)	7,36±0,09	26,76±1.04	34	60

bladder peroperatively. The bladder had fulfilled with SF until the first urine dropped from external meatus and the pressure at this time was measured by CVP monitor. Urine was obtained for culture and urine analysis in all rats at the time of operation. Urine pH and culture monitoring was conducted once in three months in each group. At the 8th month of the experiment all the animals were scarified under anesthesia. At the time of sacrifice the blood pH and bicarbonate levels, bladder capacity and end-filling pressure measures were performed. For the histological examination cystectomy was performed. The specimens were analyzed by light microscopy after fixing in 10% neutral buffered and staining with HE.

RESULTS

5 of 20 animals in group B died of anastomatic leak and sepsis. The preoperative and postoperative bladder capacity, end-filling pressure, blood pH and bicarbonate levels are shown in Table 1 and 2. The bladder capacity of group B animals were significantly increased in comparison with group A (control and sham). There were no meaningful differences in two groups related to blood pH, bicarbonate levels and end-filling pressure measurements. (Table 1 and 2).

Urine cultures and pH measurements were obtained in 45 of 90 attempts. All of these cultures were negative in survival rats. While aciduria developed in 34 percent of rats (15 of 45 measurements) in group B, no pH change was noted in group A. Hematuria was noted 11 percent (3 of 31 measurements) of rats in group A and 60 percent (27 of 45 measurements) in group B.

Bladder calculus was found 7 of 15 rats in group B.

Histopathologic results of each group rats are shown in Table 3. In the 15 bladder examined histologically in the group B (gastrocystoplasty) 2 had papilloma on the mucosal surface of gastric segment adjacent to the bladder (Fig 1). The bladder mucosa adjacent to the transplanted gastric patch (junctional zone) had pronounced hyperplastic (14 of 15), squamous metaplastic (11 of 15) change characterized by varying degrees of hyperplasia of the transitional epitheli-

Table 3. Summary of histological findings of each group of rats

	Group B (n=15) Gastrocystoplasty)
Transplanted Gastric Patch	
Re-epithelization	15/15
Atrophy of gastric gland	10/15
Cystic dilation of glands	10/15
Papilloma	2/15
Squamous metaplasia	4/15
Bladder adjacent to gastric patch	
Transitional epithelial hyperplasia	14/15
Squamous metaplasia	11/15
Inflammation	7/15
Bladder calculi	7/15

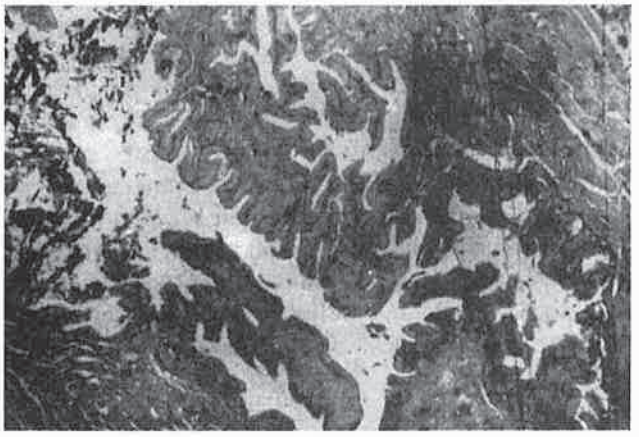

Fig. 1 . Papilloma arising from mucosal surface in area of gastric transplant. (HE20X)

Fig. 2 . The bladder mucosa adjacent to the transplanted gastric patch shows hyperplastic changes on the transitional epithelium and cystic dilatation of gastric glands. (H.E. 40X).

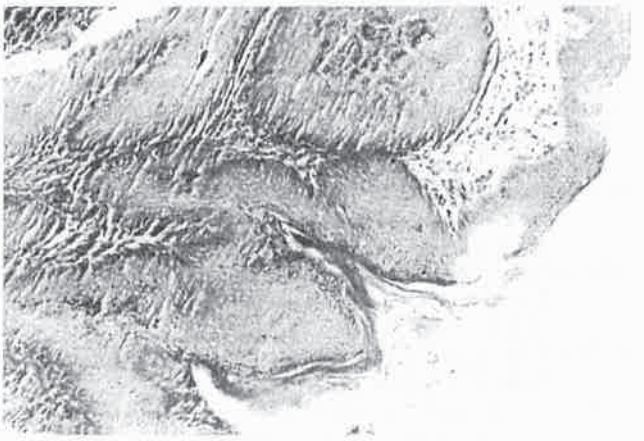

Fig. 3 . The bladder mucosa adjacent to the transplanted gastric patch has squamous metaplastic changes in varying degrees of hyperplasia of the tranitional epithelium. Also, mature ceratinization is seen on the surface of the squamous metaplastic changes (H.E. 40X).

um (Fig 2 and 3). Mild leukocytic infiltration were also seen in 7 of 15 rats in group B. No ulceration was identified in bladder or transplanted gastric segment in this group. In the sham rats bladders there were no significant changes other than occasional small suture granulomas.

DISCUSSION

Sinaiko first demonstrated the usage of gastric segment in canines(10) and than it is shown in humans(12) that a vagally denervated stomach patch can be used successfully as a bladder substitute. Further investigations by Leong(11,12) and Rudick have shown that gastrocystoplasty and gastric continent urinary reservoirs can be constructed, and they offer certain advantages over similar reconstruction's with large or small bowel. The advantages of using the stomach includes protection against hyperchloremic acidosis (due to net excretion of chloride), reduced mucus production and decreased urine infection rates(1,2,3). Also in the bladder augmentation with a segment of gastrointestinal tract, a potential complication is an undetermined risk for development of cancer. An increasing number of cases of late development of cancer in patients who underwent bladder augmentation or intestinal conduits for urinary diversion have been reported(13,14,15,16). Since bladder augmentations are frequently performed in children with long life expectancy, there is a growing concern on the carcinogenic potential of this procedure.

In our study gastrocystoplasty technique in rats and related biochemical, physiological and histopathological results were compared with control group. Biochemical results were same in each group of rats. No statistically significant differences were observed in blood pH and bicarbonate levels in each group of rats. On the other hand aciduria was noted in 34 percent of rats in group B.

The fibroelastic properties of gastric tissue have been studied by Adams(2) et al. In our study, after the gastrocystoplasty both rats in group B showed a marked increase in bladder capacity (Table 1). At the 8th month of the follow up no change in group B rats were noted as in bladder capacity increase. Also, end-filling pressure measurements were same and no statistically significant differences were observed in each group of rats.

The significant histopathologic changes were observed in group B. These changes included transitional epithelial hyperplasia (14 of 15), squamous metaplasia (11 of 15), as well as papillomas (2 of 15). No such changes were observed in the control and sham animals.

The mechanism that causes proliferative changes are unknown and numerous theories exist. Chronic bladder irritation has been shown to lead to proliferative changes in urothelium. Several groups of investigators have shown that chronic mechanical irritants are capable of inducing transitional epithelial hyperplasia, squamous metaplasia, papillomas and even carcinoma in rodents bladders(17). It has been shown that urinary tract infection in rodent bladders is associated with urothelial proliferation's(18). All animals in our study had no positive urine culture at the time of sacrifice so no correlation was found between the occurrence of proliferative changes and urinary infection.

In our study, as in other reports, all proliferative changes related to bladder augmentation occur in metaplastic transitional cells in the transplanted mucosa. It is not known these proliferative changes have an increased malignant potential but it is certain that patients with bladder augmentation have a certain risk of cancer. Further animal studies of augmentation gastrocystoplasty will hopefully allow us to understand better the risk of cancer and significance of removal of mucosa.

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CALICEAL STONES; FATE OF SHOCK WAVE THERAPY WITH RESPECT TO STONE LOCALIZATION

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SUMMARY

In a retrospective analysis, results of extracorporeal shock wave lithotripsy (ESWL) treatment were evaluated in patients with renal stones according to caliceal localization of treated stones.

198 patients underwent ESWL with the Dornier MPL 9000 were analyzed in regard to the success rate, complication rate, residual fragments, regrowth and recurrence rates. Today 210 caliceal calculus located in different portions of kidney are being comparatively evaluated.

No major complications were noted during or after ESWL. Some minor complications such as flank pain, renal colic, hematuria were observed. Flank pain was observed during ESWL treatment especially in patients with upper stones. Although stone free and residual fragment rates were similar in pelvic, upper and middle calices, patients with lower caliceal and pelvi-caliceal stones had high residual fragment rate and lower stone free rate. Patients with stones in the lower calices or pelvi-calices had recurrence and regrowth rates ($p<0.05$).

ESWL has been considered as the optimal treatment modality for most upper and middle caliceal stones. <Patients with lower claliceal stones often failed to eliminate the fragments, hence had high recurrence and regrowth rates.

Key Words: *Caliceal Stones, ESWL, Long-term results*

Exracorporeal shock wave lithotripsy (ESWL) has rightly been described as one of the most important developments in medicine of the twentieth century and the first choice of treatment for most renal stones. Stones treated by ESWL are most frequently located in the renal pelvis or in the lower caliceal group (1,2,3). However, stones in the different parts of calices respond to ESWL treatment in different degrees. Limited information in the literature on the long term results of ESWL according to the stone location is available (4,5). In this study, we evaluated the effectiveness of ESWL in calculi located in different part of the kidney

MATERIAL AND METHODS

Present study included patients with symptomatic urinary calculi who underwent ESWL monotherapy. Patients were treated using Dornier MPL 9000 in the İbn-i Sina Hospital-Ankara. The patients' histories and X-ray films were reviewed retrospectively. Patients with congenital anomalies of the urinary tract, a history of previous surgery for urolithiasis, apparent metabolic disorders, complete or partial staghorn calculi, multiple calculi and those treated by combined therapy with open surgery or percutaneous nephrostolithotomy were excluded from the study program.

Stones in the kidney according to the location were defined as complete staghorn, partial staghorn, pelvi-caliceal, pelvic, and caliceal (upper, middle and lower). Stone regrowth was considered to be one-third or greater increase in the diameter of the original residual size. Recurrence of stone was defined as its reappearance after a certain stone-free period on radiological studies. Stone multiplicity's were categorized in to solitary renal multiple renal.

During a 2-year period, a total of 198 patients (109 men, 89 women) with 210 renal units were reviewed. The mean age of patients was 40.4 years (range 16-69). Ninety three patients underwent for stones on the right side and 105 on the left, while 12 had bilateral stones. The mean stone diameter of patients was 1.23 cm. The mean stone diameter was 1.52 cm.

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Received: March 4, 1997 Accepted: May 21, 1997

in pelvicaliceal group while in the pelvic, middle and lower caliceal groups it was 1.15 cm. ($p<0.05$, Wilcoxon test). Stone diameter was not different among pelvic, middle and lower caliceal groups. Pelvicaliceal stones frequently located in the pelvis and lower calyx (70.5%). Stone composition was similar in all groups. Stones were most frequently calcium oxalate, calcium oxalate and calcium phosphate and calcium phosphate in composition.

All patients underwent ESWL under sedoanalgesia or phentanyl intravenously with an average of 2670 pulses (range: 600-7000) and 18 kv (range: 16-22). Temporary percutaneous nephrostomy for steinstrasse was performed in 2 patients and double J catheter in 2 patients. The mean follow-up was 45.4 months (range 32 to 53).

Follow-up examination included a physical examination, urine analysis and a plain abdominal film was taken on day after ESWL and monthly for 3 months and every 3 to 6 months thereafter.

Statistical analysis was performed by the Fisher's exact test and nonparametric Wilcoxon test.

RESULTS

Distribution of stones according to localization was shown in figure 1. Stones were frequently located in the renal pelvis and lower calyx. Total of 210 renal units undergoing ESWL monotherapy were evaluated. An average of 2.1 treatments per renal unit (range 1-5). The overall stone free and residual fragment rates were 59.6 and 34.3 % after the mean follow-up period, respectively. Although stone free and residual fragment rates were similar in pelvic, upper or middle caliceal stones, patients with lower and pelvi-caliceal stones had high residual fragment rate and lower stone free rate. Disintegration on stones was observed in 6.1 % of patients after treatment (Table 1). These patients were treated with either open surgery or percutaneous nephrostolithotomy. The overall stone regrowth and recurrence rates were 23 and 17.3 %, respectively. It was shown that the stone location played an important role in stone recurrence and regrowth after ESWL monotherapy. Patients with lower caliceal and pelvicaliceal stones had high recurrence and regrowth rates ($p<0.05$, Fisher's exact test) (table 2).

No major complications were noted during or after ESWL . Some minor complications such as flank pain, renal colic, haematuria and fever were observed. Flank pain was observed during ESWL treatment in especially patients with upper caliceal stones because of superposition of stones with lower ribs while the either minor complication rates were similar. In some patients with upper caliceal stones either energy level or shock number kept low because of severe flank pain. But the treatment wasn't discontinued in any patients because of side effects of ESWL. Flank pain or renal colic usually was well controlled by analgesics at the follow-up period. After ESWL treatment steinstrasse was observed in 16 patients (7.6 %). Ureteral catheter or percutaneous nephrostomy required in 4 patients. All steinstrasse were seen at first 3 months after ESWL. In long-term follow-up period (mean 45.4 months) no serious complication were observed.

DISCUSSION

Success after ESWL usually is defined as stone free rate or sufficient stone disintegration with residual particles less than 4 mm that will pass spontaneously. Short-term observations on rates free of stones were first reported by Schmiedt and Chaussy, with 90 per cent of the patients being without calculi at 3 months and 9.3% having residual fragments (6). They

Table 1. Stone free and residual fragment rates after ESWL according to stone locations

Primary Stone Location	Free of Stone After followup* (%)	Residual Fragments after followup* (%)	Lack of Disintegration (%)
Renal Pelvis	66.3	27.8	5.7
Upper calyx	69.4	15	7.6
Middle calyx	67.5	22	10.5
Lower calyx	47.8	47.8	4.34
Pelvicaly	30	60	10
overall rates	59.6	34.3	6.1

* mean 45.4 months

Table 2. Stone recurrence and regrowth rates after ESWL according to stone location

Primary Stone Location	Recurrence after follow-up* (%)	Regrowth after follow-up* (%)
Renal Pelvis	12	14.2
Upper calyx	15.3	3.1
Middle calyx	14.1	4.2
Lower calyx	27*	36*
Pelvicaly	40*	50*
Overall ratés	17.3	23

* $p<0.05$

excluded the patients with multiple stones and concomitant infection. These patients represent a highly selected patient populations with a very short follow-up period. Several report with short-term follow-up in the literature suggest a less favorable prognosis in an unselected patient population with rates free of stones of 68 to 79 percent (7,8,9). Our own long-term follow-up data (mean 45.4 months) is not comparable results with a 59.6% rate. Our results suggest that the success rate of ESWL treatment may change in long-term period.

ESWL has been reported as an effective treatment modality for pelvic, upper or middle caliceal stones. Graff and associated found that patients with lower caliceal stones had the worst success rate of 57.8%, that although patients with stones in the renal pelvis, upper and middle calices had the highest rate free of stones after the 19.1 months follow-up period (1). Similar results were obtained from different centers (3,7). In our series, the success rate for lower caliceal stones (47.8) was disappointing but not unexpectedly low. Similar results were obtained from the patients with stones that located in the pelvis and a calyx (30%). The low success rate in our study can be explained by that the pelvicaliceal stones usually extend to lower calyx (70.5%) and have larger mean stone diameter than caliceal groups.

In our series, the recurrence rate of renal pelvic stones was only 12%. But increased to 15.3 and 14.1% after treatment of stones in superior and middle calyces and reached 27% renal units with respect to stone location yielded the highest recurrence and regrowth rates of stones in lower calyx and pelvi-calyx region of kidney. Zanetti and associated reported that the recurrence rates for lower caliceal and pyelocalyceal stones were 28.6 and 31.6% respectively in average 42 months (10). These results were not different from our results. Yu et al. also reported the high recurrence and regrowth rate in the lower caliceal (27, 41% respectively) and pyelo-caliceal stones (22.2, 33.3 respectively) in their study group (2). In their gro-

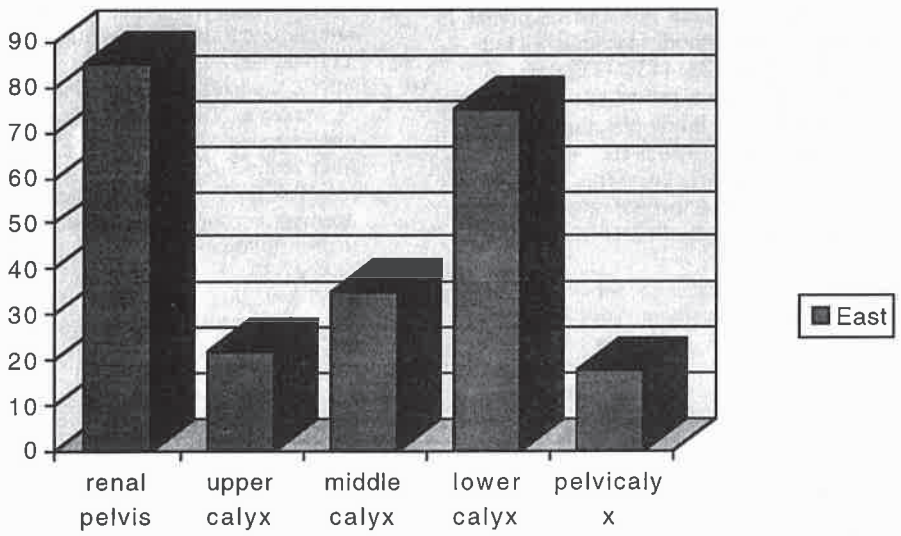

Fig. 1. Distributions of stones according to stone location.

up, patients with stones in the middle calyx had also high recurrence (22%) and regrowth (28%) rate. Those results were different from ours and Zanetti's results. But their patient group (89 patient) was small and follow-up period (75.8 months) was longer than ours. Those results suggest that the patients with stones of lower calyx often failed to eliminate the fragments and hence had high recurrence and regrowth rates. In some study it was reported that phsycotherapy with specific position and vibration massage may benefit the passage of lower caliceal residual stones in particular and appropriate medical therapy may control active stone formation in patients with or without residual stone fragments following ESWL (11, 12). The stone recurrence and regrowth rates were also higher for pelvicaliceal stones than calculi in the other upper urinary system. Close follow-up in patients with lower caliceal or pelvicaliceal stones is recommended because of high recurrence and regrowth rate. And we agreed that stone location could be play an important role in the progression of stone.

In summary, in long term follow-up period ESWL has been considered the optimal treatment for most upper urinary tract calculi with minimal side effects. It is especially effective in patients with pelvic, middle and upper caliceal stones. The residual stone rate increased as lower caliceal and pelvicaliceal stones in long term period. Our data also demonstrated that both the stone recurrence and regrowth rates after ESWL were influenced by the stone location. Patients with stones in the lower calyx or pelvicalyx had high recurrence and regrowth rates after ESWL. When compared with other upper tract stones. We agreed that in these patient close follow-up, assistance treatment modalities such as physiotherapy or vibration massage and appropriate medical therapy should be used for reducing the recurrence and regrowth rate.

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MYXOMAS

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SUMMARY

Between Ocober 1, 1990 and December 31, 1996. Five patients have undergone excision of a cardiac myxoma, which was located in the left atrium in 3, in the right atrium in 2. There were 3 female and 2 male patients with a mean age of 35.4 years (range, 17 to 64). Peripheric arterial embolism was seen in two left atrial myxoma cases. One of these patients also had myocardial infarcion due to coronary embolism. There was no operative death. Mean follow-up was 17.2 months (range, 6 to 42 months). No instances of tumor recurrence were observed. All patients were in New York Heart Association class I or II in the postoperative period.

Key Words: *Surgical treatment, myxoma*

Cardiac myxoma is the most common primary tumor of the heart (1-8). The diagnosis of myxoma is rarely made on clinical grounds because there are no specific historical, physical examination, chest x-ray, or electrocardiographic findings. Since the introduction of echocardiography, most cases of myxoma are diagnosid during life and potentially curative surgical extirpation is thus possible (4,6).

PATIENTS AND METHODS

Five patients (3 women and 2 men) underwent operations for cardiac myxoma from October 1, 1990 to December 31, 1996 in Cardiovascular Surgery Department of Erciyes University Medical School. The average patient age at operation was 35.4 years (17 to 64). Three of the tumors were found in the left atrium, 2 in the right atrium. In one case, which myxoma was in the left atria, there was also thrombus in the right atrial cavity.

The primary symptoms at presentation were shortness of breath in 4 patients, palpitations in 5, weakness in 2, fatigue in 2, peripheric arterial embolism in 2. Myocardial infarction due to coronary embolism was seen in one of left atrial myxoma cases which also had peripheric embolism. Nearly every patient had multiple symptoms.

Physical findings were generally nonspecific, but 3 patients had an audible murmur: systolic in 1 and diastolic in 2.

Diagnosis were obtained by transthoracic and transosefageal echocardiography (Fig. 1,2). Catheterization was made in the case which myocardial infarction was seen (Fig. 3,4). Neither chest radiography nor electrocardiography was determinant for the diagnosis.Electrocardiography showed sinusal tachycardia in 3 cases, and V3-pour R, V4-6 QS in 1 (Fig. 5).

One patient had anemia (hemoglobin level less than 10 g/dl). An elevated sedimentation rate was noted in 3 of 5 patients.

Surgical technique: A median sternotomy incision was employed in all patients. Operation was performed with moderately hypothermic cardiopulmonary bypass, topical cooling and cold potassium cardioplegia. Both the superior vena cava and the inferior vena cava were routinely cannulated separately through the right atrium regardless of the position of the myxoma, with care taken to avoid any undue manipulation of the heart. Right atrial myxomas were resected through a right atriotomy. Two of the left atrial myxomas were excised through a left atriotomy. In one case, thrombus was resected through right atrial incision and transseptal incision was made to excise left atrial myxoma. In the same case apical thrombectomy and

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Received: Mar 14, 1997 Accepted: Aug 14, 1997

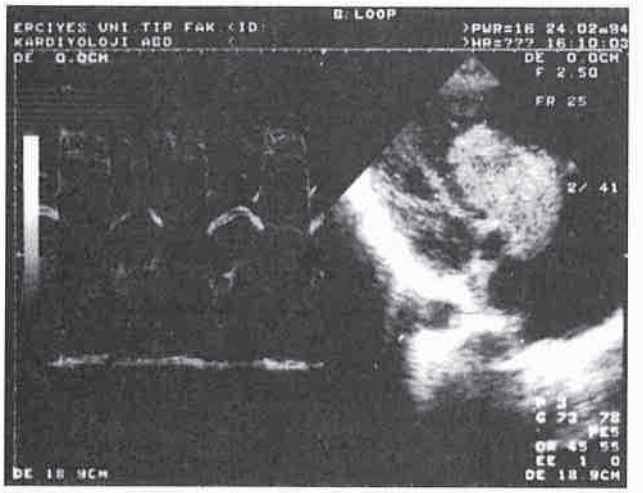

Fig. 1. Echocardiographic view of a large right atrial myxoma during diastole.

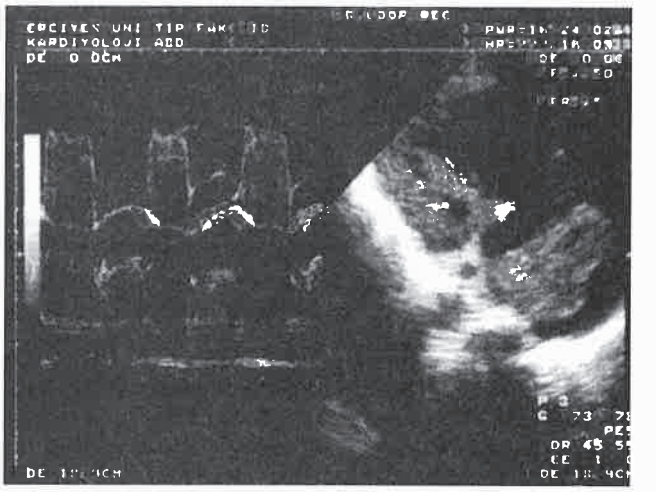

Fig. 2. Echocardiographic view of a large right atrial myxoma during sistole.

linear plication were performed for left ventricular aneurysm. In two patients, who had also peripheric embolism, both tumor excision and Fogarty balloon catheter embolectomy were performed. En bloc excision with complete resection of the pedicle was performed in all patients. All surviving patients underwent physical examination, electrocardiography, and echocardiography.

RESULTS

Follow-up of patients was at a mean duration of 17.2 months (range, 6 to 42 months) after myxoma resection.

There were no operative death. Only morbidity included syme amputation in 1 patients who had arterial embolism. All patients were in New York Heart Association class I or II, and no recurrences have been documented after operation.

DISCUSSION

Cardiac myxoma is the most common primary benign caridac tumor and accounts for approximately 50% of all such lesions (1-12). These tumors have been encountered in all age-groups; the majority, however, are diagnosed between the third and sixth decades of life (4,6,8,9). They seem to occur more frequently in women and are rare in children (4,6,9). Familial myxomas have been reported (4,6,13). In our cases male-to-female ratio was 2/3 and 4 of the patients are diagnosed betwen the third and sixth decades.

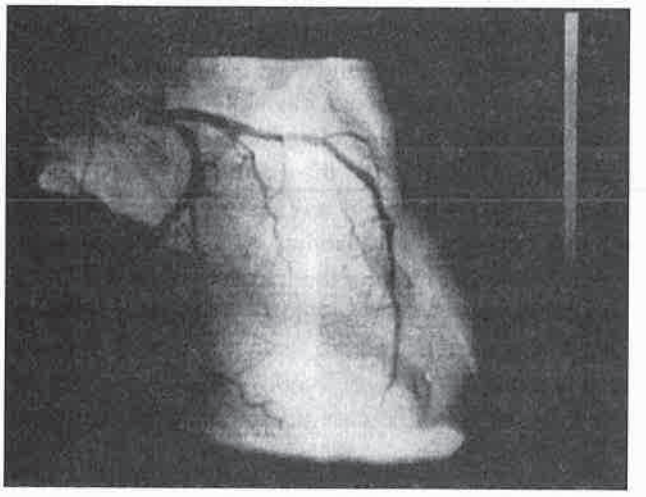

Fig. 3. Coronary arteriography of the patient with left atrial myxoma who had also myocardial infarction and left ventricular aneurism.

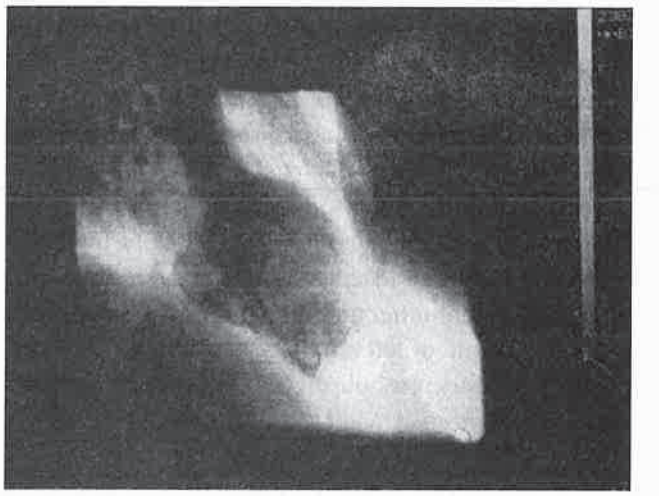

Fig. 4. Left ventriculography of the patient ith left atrial myxoma who had also myocardial infarction and left ventricular aneurism.

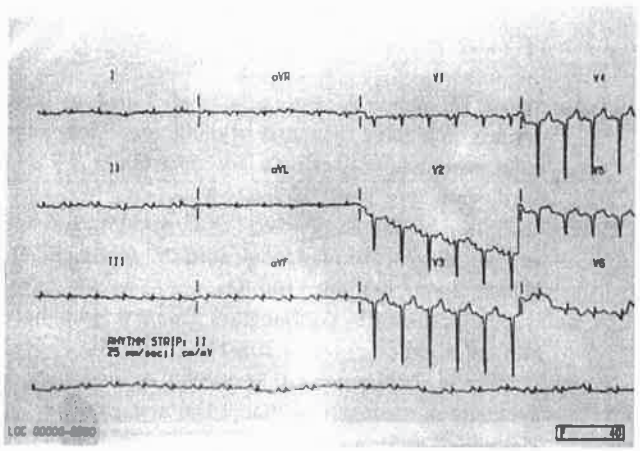

Fig. 5. Electrocardiography of the same patient.

The literature frequently quotes a 75% incidence of left atrial myxomas, a 20% incidence of right atrial myxomas and a 5% incidence of ventricular myxomas (1-6,9,14). Myxomas are usually single but multiple tumors have been reported and multiple chambers may be involved (4-6,9). Their size has varied from several millimeters to over 10 cm in diameter (5,6).

The classic triad of symptoms relates to the obstructive, embolic, and constitutional effects of the tumor (3,4,6,9,10). The duration of symptoms depends on the rate of growth of the tumor (6).

Obstructive symptoms occur in 54 to 95% of patients symptoms include positional dyspnea, orthopnea, paroxymal nocturnal dyspnea, an fatigue. Syncope is rarely seen and may be the result of complete transitory obstuction of the cardiac valve (4,5,6,9). On physical examination, the signs of left atrial myxoma also mimic mitral stenosis and insufficiency (6,15). In our patients, two had symptoms of mitral valve disease, and the other had symptoms of tricuspid valve disease.

Systemic emboli are the second arm of the classic triad and occur in 20 to 60% of patients with myxomas (4,6,10,11,16). Fifty percent of myxomatous emboli from the left heart go to the central nervous system, but they can embolize to any arterial bed. The symptoms and signs are related to the vascular bed that is occluded and can not be distinguished from acute arterial insufficiency of other etiologies. The diagnosis of a myxoma can be made by histologic examination of the removed embolized material (4,6,9)). There were symptoms and signs of emboli due to myxoma in our 2 cases: One in the only left leg, the other in the right upper and both right and left lower extremities. The last patients had also coronary embolism.

The constitutional manifestations, which occur in over 90% of patients, are due to the presence of the tumor and are independent of the location of the tumor (4,6). These signs and symptoms include myalgia, muscle weakness, artralgia, fever, weight loss, fatigue, Raynould's phenomenon, clubbing, leukocytosis, thrombocytopenia, anemia, an elevated sedimentation rate, increased serum gammaglobulins (4,6). Fever, weakness, fatigue and anemia were the constitutional-symptoms in our patients.

The chest roentgenogram and the electrocardiographic findings in patients with myxoma are nonspecific and reflect changes in chamber size and hypertrophy of the chamber walls. The majority of the patients are in normal sinus rhythm, although atrial fibrillation or flutter, low voltage, right bundle branch block are sometimes encountered (4,6).

Echocardiography presently is the most preferred laboratory technique for diagnosis of cardiac myxomas. Angiocardiography is rarely required for diagnosis or for preoperative surgical guidance (4,6,11,17-19).

Myxomas are potentially lethal benign neoplasm that may be associated with local and systemic complications (4). Because rapid deterioration and sudden death may occur early, surgical removal is indicated once the diagnosis of myxoma is made (5,7,15,17).

The treatment of chose is prompt surgical resection, both for symptomatic improvement and to avoid complications. To avoid recurrences, the aim of operation should be to remove not only whole mass but also its base of attachment (1,6).

Myxomas are easily resectable, and the surgical mortality in many studies has fallen below 5% (2,3,5,8,14,20). There were no operative deaths. All patients were in New York Heart Association class I or II after operation.

Intracardiac recurrence of myxoma has been reported at rate of 0 to 14% (3-6,8). Periodic echocardiography is recommended for follow-up to screen for intracardiac recurrence. No patients has developed clinical signs of myxoma recurrence in our cases.

In conclusion, the extended follow-up of patients with myxomas shows that excision of such tumor is curative and the long-term outcome excellent. Regardless of their location, myxomas should always be resected.

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DETECTION OF RECALLING MUSIC AND INFLUENCE ON PATIENTS STRESS STATUS IN CARDIAC SURGERY

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SUMMARY

In cardiac surgery the high incidence of recalling events have been (0.5%-23%)reported. In this study we aimed to evaluate postoperative recalling and to assess the protective effect of music on postoperative stress in cardiac patients. A total of 5 patients (8.3%) remembered the operative actions, music and speeches. Self-Assesment and Beck-Depression test did not show difference between music exposure and non-exposure groups.

We concluded that perioperative music did not protect the patients from postoperative stress response. This result may be due to the preoperative awareness of patients that they would listen to music so that they might be given extra stress.

Key Words: *Anesthesia, Intraoperative awareness, Posttraumatic stress syndrome*

Intraoperative awareness has become an interesting and popular issue because of many applications of several new anesthetic drugs. In spite of the fact that intraoperative awareness may vary among different patient populations, the auditory stimuli has long been known as the most prevalent perception during general anesthesia (1,2). A very high incidence of postoperative recall (0.5% - 23%) can be observed in patients in cardiac surgery (3,4,5). This intraoperative awareness may cause post-traumattic stress disorder and uncomfortable postoperative recovery (3,6,7,8,9).

The aim of this study were to determine the postoperative recalling in cardiac surgery patients and to assess the protective effect of music exposure during anesthesia on postoperative stress and well being of the patients.

PATIENTS AND METODS

Patients who would undergo elective cardiac surgery were asked to participate in this study. Sixty patients of ASA physical status III were included.

The first group (n=30) were asked their favorite kind of music and informed that they would listen to musical pieces intraoperatively. The second group (n=30) were not informed that they would listen to musical pieces and did not have headphones during anesthesia.

All patients were premedicated with intramuscular (I.M.) 0.05-0.1 mg/kg Morphine and 0.1 mg/kg Diazepam. For induction intravenous (I.V.) 0.3 mg/kg Midazolam, 10 mg/kg Fentanyl and 0.15 mg/kg Pavulon were given.

Simultaneously 100% owygen was given. Anesthesia was maintained with 3 mg/kg Fentanyl and 0.05 mg/kg Midazolam per half an hour and during Cardiopulmonary bypass (CPB) 2 mg/kg Fentanyl and 0.05 mg/kg Midazolam per half an hour.

On the seventh postoperative day all patient were asked about the noticed sound perceptions particularly the music, pain, intubation tube and how did they remember feeling in recovery (Table 1). Preope-

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Received: June 9, 1997 Accepted: July 17, 1997

Table 1: Interview Questionare

1. Orientation of time and place
2. Cooperation
3. Additional problem?
4. Do you remember the operation?
5. Did you feel tracheal entubation?
6. Did you feel pain?
7. Did you hear voices?
8. Did you hear music?
9. What kind of music did you hear?
10. How long did you hear the music and how did you feel?
11. How did you remember feeling in recovery?
12. How do you assess this method?

ratively and postoperatively we evaluated patient stress response by using Beck-Depression and Self-Assesment Tests.

All the collected data were analyzed by the t test.

RESULTS

Three patients (10%) in the first group recalled the exact music and name of signes and the band. In the second group two patients (6.7%). Who didnot listen to the music recalled some intraoperative events such as sternotomy, surgeons voice and words. The difference of recalling was not statistically significant between 2 groups ($p>0.5$). Nopatient complained of peroperative pain despite 8.3% of them remember the operative actions, music and speeches.

The self assesment test didnot show difference between preoperatively and postoperatively in both groups but the differnces between preoperative and postoperative results of Beck-Depression test were statistically significant in the first and second group at at $p=0.024$ and $p=0.035$ respectively. Both test were not different when assessing preoperative or postoperative results between 2 groups. Preoperatively p value was found att 0.583 for Self Assesment test and 0.493 for Beck Depression test. The postoperative Self Assesment test showed no significant difference postoperatively between 2 groups ($p= 0.489$), as in the Beck-Depression test ($p= 0.789$). Those data indicated that perioperative music didnot protect the patients from postoperative stress response.

DISCUSSION

Our results indicated that patients who were given anesthesia for cardiac surgery with Fentanyl-Miadazolam combination may perceive the events taking place at operating room.

Remembering the intraoperative events has been a well known entity and the incidence is reported as 0.1-3.8% (10,11). However the incidence can be much higher in cardiac anesthesia as 23% (3). Recalling intraoperative events is not related to the different types and dosage of intravenous agents (Ketamin, high dose Fentanyl, Propofol, Benzodiazepines) and inhalation agents (6, 12-14). Some reports indicate that in near-complete depression of cortical electrical activity by Thiopentone or Isoflurane in animals and humans, there may be some movement in respons to stimulus (13,15). This suggests that even with deep anesthesia there may be some perception in response to stimuli and this may be controlled by subcortical centers during anesthesia. This sftatus may be coexistent with intraoperative awareness during anethesia, so we cannot predict the depth of desired anesthesia for each case (13,15,16).

Intraoperative awareness may cause posttraumatic neutosis (3,6-9) In a study, auditory perception and the sensation of paralysis were most frequently mentioned, followed by the sensation of pain. Patients feeling were mostly related to anxiety, panic, powerlessness and helplessness and 70% of them experienced unpleasent aftereffects, including sleep disturbances, dreams and nightmares and flashbacks (6).

Cobcroft and et all. studied 187 patients who suffered awareness during general anesthesia and the findings show a disturbing symptomatology ranging over almost all modalities of sensation and of postoperative psychological and pyschiatric disturbances (9).

In this study, the preoperative Beck-Depression test results showed slight depression in postoperative period. As we did not observe a great deviation of the postoperative patient stress status from preoperative tests we think the anesthesia was sufficient. Because we told the patients in the first group that they would listen to music, it may cause a stress factor so that the non-music and music group did not show difference according to pschological stress test results.

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HEREDITARY PANCREATITIS: REPORT OF A FAMILY FROM TURKEY*

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SUMMARY

Chronic pancreatitis is a rare disease in children and is usually secondary to underlying diseases such as hereditary pancreatitis, cystic fibrosis, hyperlipidemia, prolonged malnutrition, gallstones or anomalies of the biliary pancreatic duct system. Hereditary pancreatitis is a common cause of chronic pancreatitis in children; but often unrecognized until months to years later. We report a family with hereditary pancreatitis in which four members are affected.

Key Words: *Abdominal pain - childhood - chronic pancreatitis - hereditary pancreatitis*

Although rare in children, disorders of the pancreas may lead to significant morbidity and mortality. Acute pancreatitis is unusual in pediatric patients, and chronic pancreatitis is even less common. Among the etiologic factors, hereditary pancreatitis is one of the most common cause of chronic pancreatitis in children. Hereditary pancreatitis presents in childhood but diagnosis usually delays for months or years. The disease is transmitted in an autosomal dominant manner with incomplete penetrance. The most common symptom is recurrent attacks of abdominal pain, which later may result in exocrine and/or endocrine pancreatic insufficiency (1). A family with hereditary pancreatitis with four affected members are presented here.

CASE REPORT

I- Case I (Index case)

A 12-yr-old boy was admitted to our pediatric gastro-enterology clinic in Ankara because of severe epigastric pain, vomiting and weight loss of six months' duration. He had been well and healthy before his symptoms developed. There was no history of trauma or drug consumption. His mother and father, 34 and 35 years old respectively, were well and healthy and there was no consanguity between them. His 10-yr-old sister had an operation for pancreatic pseudocyst 5 years ago. Physical examination were within normal limits except for abdominal tenderness with deep palpation. Laboratory findings on admission were as follows: Complete blood count normal, ESR 25 mm/h, CRP (-), fibrinogen: 248 mg/dl, urine and stool examinations and cultures were normal. BUN, electrolytes, glucose, calcium, creatinine phosphokinase, AST, ALT, amylase and lipase were all normal. Abdominal plain X-ray as well as a barium swallow showed no abnormalities. An abdominal ultrasound on admission showed a solitary cystic mass within the head of the pancreas (Figure 1). For further evaluation, ERCP was performed which showed a dilated pancreatic duct with a pseudo-cyst in the localization of the head of the pancreas (Figure 2). With these findings, pancreatic pseudocyst as a result of recurrent attacks of chronic pancreatitis was diagnosed. Etiologic evalution revealed normal serum lipid profile and normal sweat chloride test. He was treated with a somatostatin analogue for a short period of time and as the pseudocyst did not resolve, endoscopic papillotomy was performed with the placement of pancreatic stent. He is still receiving pancreatic enzyme replacement theraphy. He has minimal symptoms, gained weight and

* This paper was presented and published as an abstract at XII. Ulusal Gastroentereloji Kongresi, 25-30 September 1995, İzmir

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Received: Nov 28, 1996 Accepted: July 17, 1997

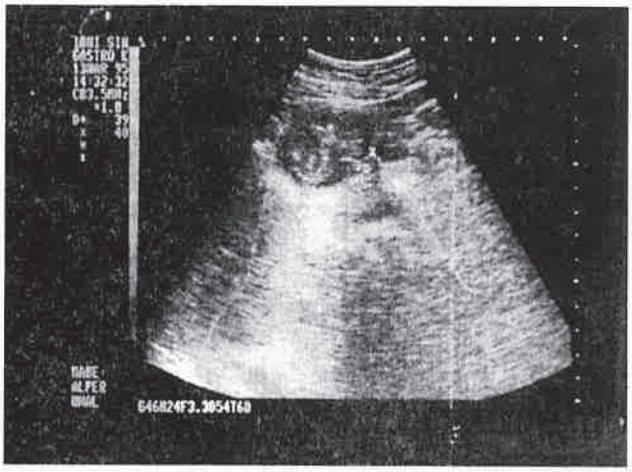

Fig. 1. Abdominal ultrasound of index case on admission showing a solitary cystic mass within the head of the pancreas.

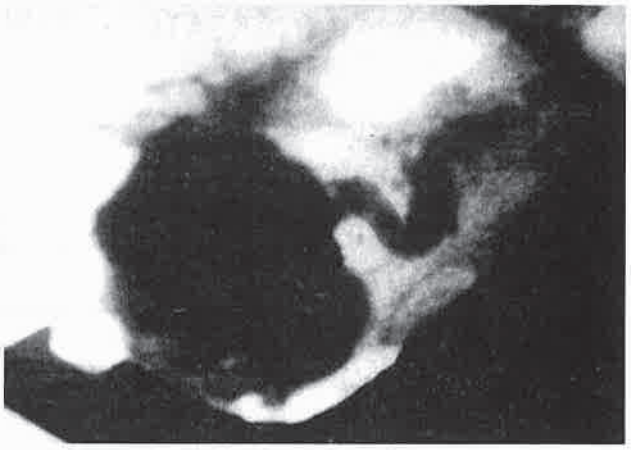

Fig. 2. ERCP of index case showing a dilated pancreatic duct with a pseudocyst in the localization of the head of the pancreas.

ultrasonographic and tomographic examination showed no pancreatic pseudocyst residue, but pancreatic duct dilatation persists (Figure 3).

II- Case II (Sister of case I)

10 yr-old-sister of the index case had recurrent attacks of abdominal pain since she was 3 and had an operation for pancreatic pseudocyst when she was 5 years old. She remained mildly symptomatic after the operation and the present laboratory and radiologic evaluation including ultrasound and computerized tomography was normal.

III- Case III (Mother's sister of case I)

The mother's sister was 21 years old and she had several episodes of severe abdominal pain since childhood. Her medical history included right pleural effusion and pleuritis at age 19 during which no specific etiology was found and resolved without a specific theraphy. Her serum amylase level was 251 U/L (reference range, 25 to 125). Ultrasonographic examination revealed pancreatic duct dilation with multipl echogenicities wich were confirmed to be calcifications within the pancreatic duct and paranchyma with computerized tomography and ERCP.

IV- Case IV (Mother's brother of case I)

The mother's brother of case I, who was 19 years old had several episodes of abdominal pain since childhood. Familial Mediterrenean Fever was diagnosed based on this history, but he had only partial relief of abdominal pain when receiving Colchicine. His laboratory findings were within normal limits but an ultrasonographic examination as well as ERCP revealed multipl pancreatic calcifications.

DISCUSSION

Chronic pancreatitis is a rare disease in children and is usually secondary to underlying diseases such as hereditary pancreatitis, cystic fibrosis, hyperlipidemia, prolonged malnutrition, gallstones or anomalies of the biliary-pancreatic duct system. The most common manifestation is repeated attacks of acute pancreatitis (1).

Hereditary pancreatitis is a common cause of chronic pancreatitis in pediatric patients. In order to confirm the diagnosis, at least two other family members must share similar symptoms and episodes of abdominal pain must be traced to childhood without ot-

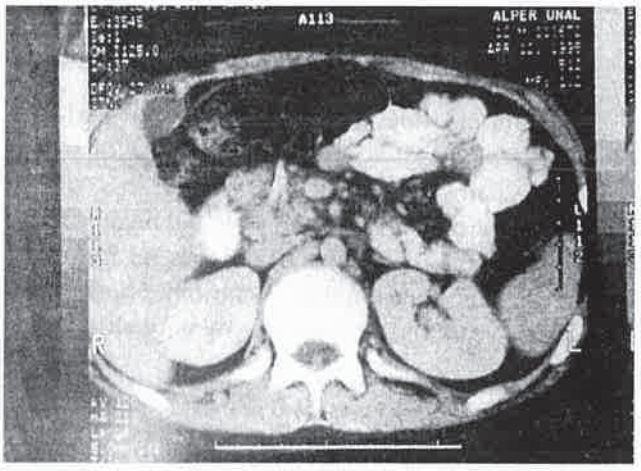

Fig. 3 Abdominal tomography of index case after endoscopic papillotomy was performed, showing persistence of pancreatic duct dilatation.

her etiologic factors (1,2). This entity, is inherited as an autosomal dominant trait with incomplete penetrance.

All the family members presented here manifested the disease as repeated attacks of acute pancreatitis which is the most common symptom (1). They had no signs of malabsorbtion or endocrin pancreatic insufficiency.

Among the laboraty findings of the index case (Case I), serum amylase and lipase values were within normal limits. This is suggested to be due to progressive loss of acinar mass in advanced disease (3).

Hereditary pancreatitis is frequently characterized by occurence of a number of calcifications scattered along the main pancreatic duct (4). Within this family of hereditary pancreatitis reported here, two of them (case III and IV) had calcifications within the pancreatic duct and paranchyma.

Hereditary pancreatitis may present with an acute episode of pleural effusion (5). Pleural effusion in the medical history of the mother's sister of the index case was probably due to an attack of pancreatitis.

Pancreatic pseudocyts, occur commonly in hereditary pancreatitis, with an estimated incidence in upto 50% of patients which are localised collections of necrotic debris that develop following autodigestion of the pancreas (6). Among these four cases reported here, two of them developed this complication. For those, that do not resolve within six weeks, treatment is often mandatory since the rate of complications such as infection, obstruction, rupture and hemorrhage is high (7). The different therapeutic modalities for draining the pseudocysts include surgical drainage, percutaneus drainage and applying a somatostatin analogue (8). Endoscope guided drainage and placement of a stent is a relatively new modality for the treament of pancreatic pseudocysts which we performed to our index case (9).

In conclusion, we report a family with hereditary pancreatitis from Turkey. Two pediatric and two adult patients are discussed. Chronic and recurrent abdominal pain in children shoud alert the physician to the possibility of chronic pancreatitis. Standard biochemical tests, such as serum amylase and lipase, may be normal, and if pancreatitis is clinically suspected, additional evaluation by ultrasonography will help to identify most patients. When a young patient presents with pancreatitis, hereditary pancreatitis must be considered because it is a common cause of pancreatitis in children and its clinical features are indistinguishable from other causes (1). ERCP should be performed to each patient to detect structural abnormalities that may be relieved by surgery. Therapeutic approach for hereditary pancreatitis is the same as for non-hereditary pancreatitis but early diagnosis and treatment of hereditary pancreatitis can improve the associated clinical outcome and morbidity.

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SYMPTOMATIC CAVERNOUS ANGIOMAS EXTENDING INTO THE LATERAL VENTRICLE REPORT OF THREE CASES

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SUMMARY

The clinical, neuroradiological and histopathological features of cavernous angiomas of the lateral ventricle are presented, based on an analysis of symptomatic, histopathologically verified three cases. Three cases were admitted with clinical evidence of haemorrhage. The vascular malformations were also totally excised in these three cases. All of cases were uneventful in the postoperative stage.

Key Words: *Cavernous angiomas, Lateral ventricle, Magnetic resonance imaging, Surgery*

Vascular malformations consist of arteriovenous malformation, telengiectasia, cavernous angioma and venous angioma (1). Intracranial cavernous angioma is a relatively rare lesion. They comprise 5 to 13 % of central nervous system vascular anomalies (2,3,4,5).

In this study, we report three cases with cavernous angioma of the lateral ventricle that seen rarely.

CASE REPORTS

These cases have been summarized in Table 1 and Table 2.

CASE 1. A 30-year-old man admitted with headache and vomitig presenting 7 days. Neurological examination was normal. Computerized tomographic (CT) scan without contrast media revealed a hyperdense lesion within the left dilated lateral ventricle (Fig.1). T1-weighted magnetic resonance imaging (MRI) showed a hyperintense lesion of the left lateral ventricle (Fig. 2A, 2B). T2-weighted MRI demonstrated a lesion consist of hyperintense and surrounding hypointense ring in the left lateral ventricle (Fig.3A, 3B). Digital subtraction angiography (DSA) was normal.

Operation: Under the general anaesthesia, the left temporoparietal craniotomy was performed. Haematoma was evacuated. Lateral ventricle was opened, and vascular malformation was totally excised by microsurgical technique. Postoperative CT scan confir-

Table 1: Clinical and radiological findings of three cases with cavernous angiomas of the lateral ventricle

Case	Sex	Age	Symptom	Period	CT	MRI	DSA	Follow-up	Localization
1	M	30	headache vomiting	7 days	+	+	+	3 months	L,LV
2	M	30	headache numbness	4 years	+	+	+	6 months	L,LV
3	M	18	headache vomiting	1 month	+	-	-	12 months	R, LV

Abbreviation: M: Male, L: Left, R: Right, LV: Lateral ventricle.

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Received: Fab 7, 1995 Accepted: May 21, 1997

Table 2: Results of surgical treatment and follow-up of three cases with cavernous angiomas of the lateral ventricle

Case	Surgical excision	Result	Follow-up period
1	Total	Good	3 months
2	Total	Good	6 months
3	Total	Good	12 months

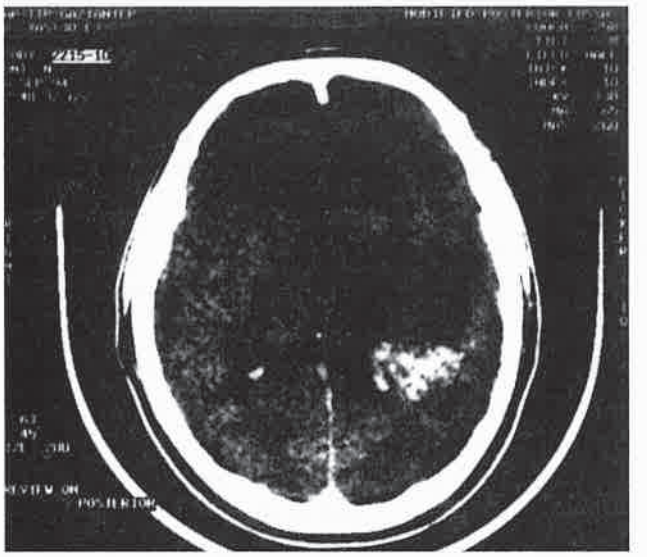

Figure 1: CT scan without contrast media showing a hyperdense lesion within the left dilated lateral ventricle.

med total excision of the vascular malformation of the lateral ventricle (Fig. 4). Histopathological examination was cavernous angioma. Postoperative period was uneventful. The patient was good three months after the operation.

CASE 2. A 30-year-old man admitted with headache and numbness in the right side of his body presenting four years. His neurological examination revealed a right-sided sensory deficit. CT scan without contrast media demonstrated a hyperdense lesion in the left lateral ventricle (Fig.5). T1-weighted MRI showed a hyperintense lesion in the lateral ventricle (Fig.6A). T2-weighted MRI demonstrated a lesion consisted of hyperintense and surrounding hypointense ring (Fig.6B). DSA was normal.

Operation: Under the general anaesthesia, a left parietoocipital craniotomy was performed. Haematoma was drained. Lateral ventricle was opened. Vascular malformation of the lateral ventricle was totally excised by microsurgical technique. Postoperative stage

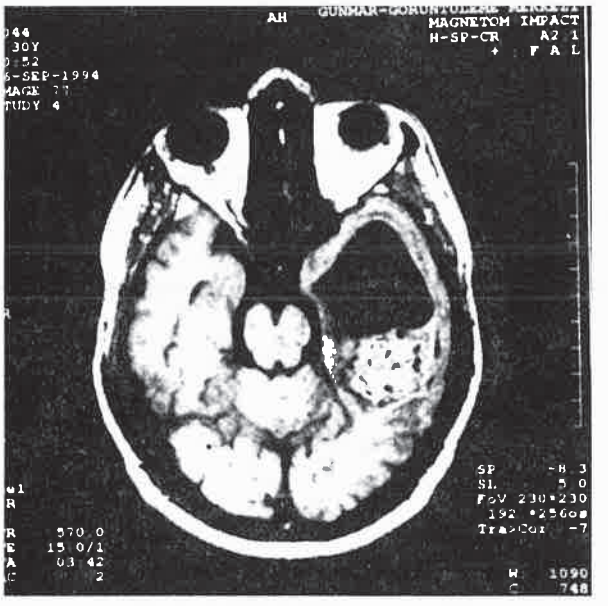

Figure 2A: Axial (Fig.2A) and sagittal (Fig.2B) T1-weighted MRI demonstrated a hyperintense lesion of the left lateral ventricle.

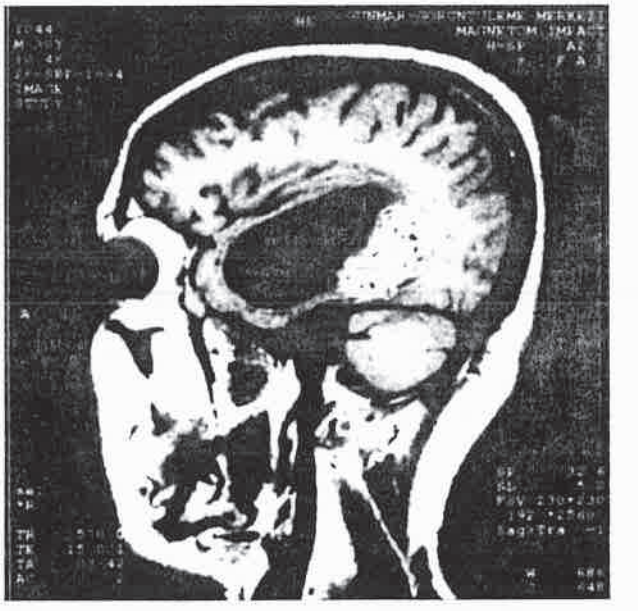

Figure 2B: Axial (Fig.2A) and sagittal (Fig.2B) T1-weighted MRI demonstrated a hyperintense lesion of the left lateral ventricle.

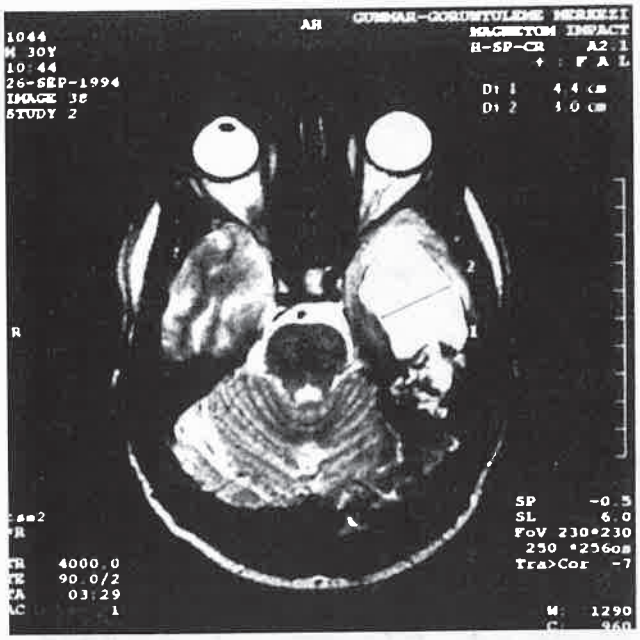

Figure 3A: Axial (Fig.3A) and coronal (Fig.3B) T2-weighted MRI showing a lesion consisted of hyperintense and surrounding hypointense ring.

Figure 3A: Axial (Fig.3A) and coronal (Fig.3B) T2-weighted MRI showing a lesion consisted of hyperintense and surrounding hypointense ring.

did not any problem. Histopathologically examination confirmed cavernous angioma. Control CT scan without and with contrast media showed that vascular malformation expanding into the lateral ventricle was totally removed (Fig. 7A, 7B). The patient was good 6 months after the surgery.

CASE 3. A 18-year-old man admitted with headache and vomiting presenting one month. The patient's neurological examination was normal. CT scan without contrast media demonstrated a hyperdense lesion of the right lateral ventricle.

Operation: Under the general anaesthesia, a right parietooccipital craniotomy was performed. Haematoma was drained, and lateral ventricle was opened. Vascular malformation was totally excised. The patient's neurological examination was normal in the postoperative period. But, last three weeks, the patient was gradually become bad. He had lethargy. CT scan demonstrated hydrocephalus. Therefore, medium-pressure ventriculo-peritoneal shunt operation was performed. The patient's neurological condition was progressively improved one week after the operation. The patient was good one year later.

DISCUSSION

An intraventricular localization of the supratentorial cavernous angiomas has been reported in a rate ranging from 2.5 to 14 % of cases (6). Yamasaki et al (6) reported only one case that located in the lateral ventricle in their series consisted of 27 cases with intracranial cavernous angiomas. Acciarri et al (7) reported a intraventricular localization in 4 (6%) of 74 cases with supratentorial cavernous angiomas. In their series, there was only one case of the lateral ventricle. The present study has only three cases (13 %) of the lateral ventricle, and all of the supratentorial cavernous angiomas consist of 23 cases.

The clinical manifestations of intracerebral cavernous angiomas usually consist of seizures (60-70 %), headache (20-25 %) and haemorrhage (20-25 %) (3,6,8,9,10,11,12,13). On the basis of our experience, we think that cavernous angiomas of the lateral ventricle have a greater tendency to be symptomatic from bleeding as in our three cases. Mass effect of cavernous angiomas of the lateral ventricle occurs less.

Conventional skull radiographs rarely reveal calcifications (3,14). CT scan permit radiological detection of cavernous angiomas. In scans obtained before administration of contrast media, the lesion commonly appears hyperdense, but mixed hyperdense and isodense lesions have been described (13,15,16). In this study, CT scan also demonstrated hyperdense lesion in every three cases. Mass effect, occasionally secondary to hematoma, is frequently present. Contrast media administration may improve the delineation of the le-

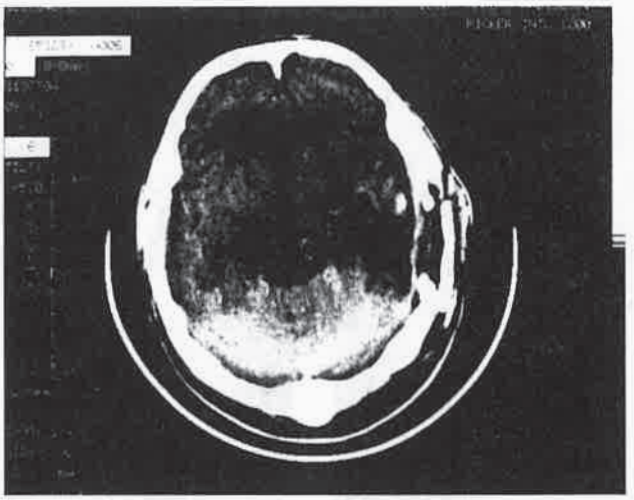

Figure 4: Postoperative axial CT scan demonstrated total excision of the cavernous angioma of the lateral ventricle.

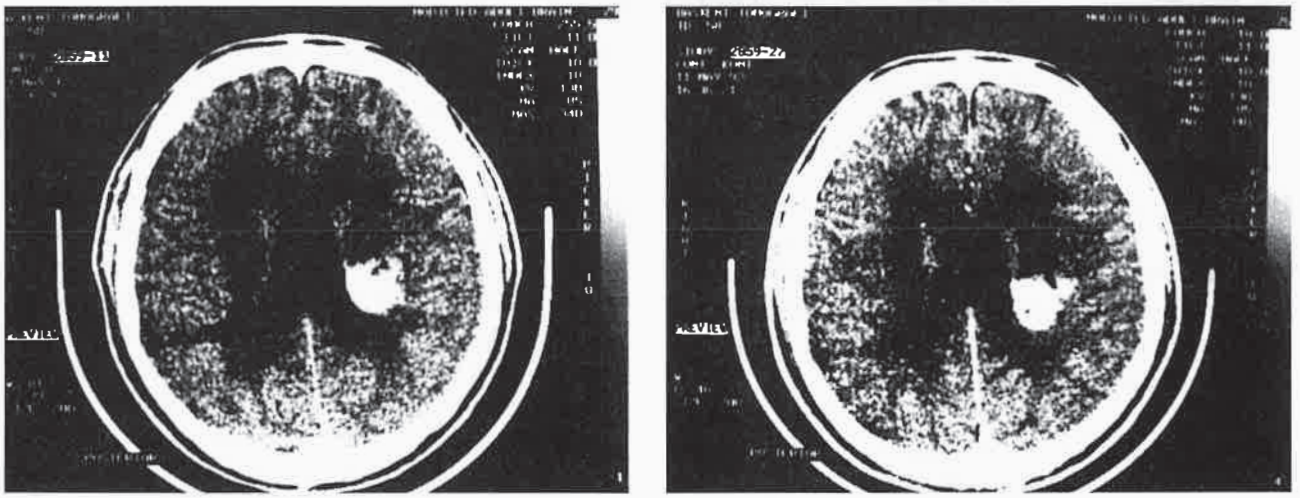

Figure 5: CT scan without contrast media (Fig 5A) and with contrast media (Fig 5B) revealed a hyperdense lesion extending into the lateral ventricle.

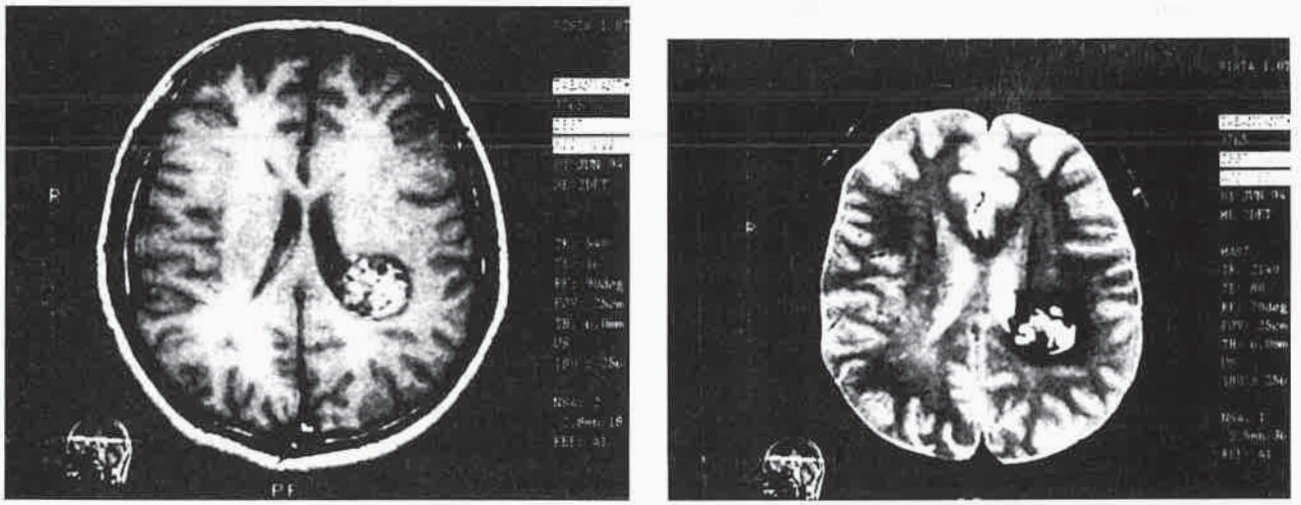

Figure 6: Axial T1-weighted (Fig.6A) and axial T2-weighted (Fig.6B) MRI demonstrated a lesion extending into the lateral ventricle.

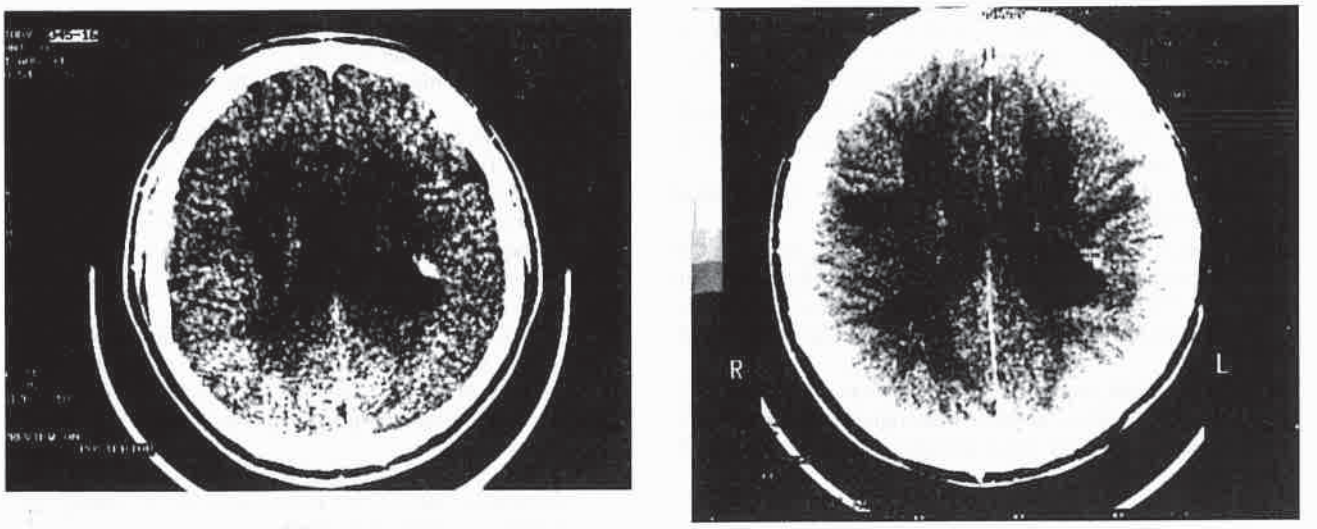

Figure 7: Control CT scan without contrast media (Fig.7A) and contrast media (Fig.7B) showed total surgical excision.

sion with faint enhancement. The preoperative diagnosis with CT scan differentiate cavernous angiomas from another lesions such as especially other vascular malformations and tumoural lesions.

The sensitivity of MRI increases the probability of detecting a cavernous angiomas. Recently MRI has also proved to be specific in the diagnosis of nature; patterns strongly suggestive of cavernous angiomas are the presence of a webbed core of mixed signal intensity ringed by a border of reduced intensity in the T2-weighted images (13,15,16,17,18), as in our cases. Angiographical findings in cavernous angiomas are quite variable. The angiograms may be normal or show only an avascular mass (12,16).

The treatment of choice for cavernous angioma is surgical removal. The aims are to eliminate mass effect, to determine the histopathological nature of the lesion, to relieve any attendant epilepsy, and to avert bleeding or rebleeding (3,7,8,9,10,11,13,14,16,19).

We operated three cases with cavernous angioma of the lateral ventricle for both to eliminate mass effect due to haemorrhage and to prevent rebleeding.

CONCLUSION

Symptomatic cavernous angiomas extending into the lateral ventricle can produce neurologic disability as a result of secondary to recurrent haemorrhage. MRI provides the definitive diagnostic tool to characterize these lesion. Total surgical removal of the vascular malformation, and evacuation of haematoma is necessary to prevent progressive and irreversible neurological deficits as in our three cases.

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IS NEAR-INFRARED SPECTROSCOPY A RELIABLE PREDICTOR OF NEUROLOGIC OUTCOME IN HYPOTHERMIC TOTAL CIRCULATORY ARREST IN HUMANS?

Neslihan Alkış* • Yeşim Ateş • Menekşe Okşar*** • Murat Sayın*** • Melek Tulunay******

SUMMARY

Near infrared spectroscopy was used to monitor continuous cerebral oxygen saturation (rSO2) during 2 cases of hypothermic cardiac arrest (HCA). HCA time was 28 minutes and 41 minutes in these cases. Desaturation did not occur during total circulatory arrest. rSO2 values decreased during rewarming in case 1, but remained above 60% in both cases. There was no neurologic impairement in case 1 postoperatively whereas case 2 died in the early postoperative period due to tumoral pulmonary embolism.

There are limited number of studies concerning continuous spectroscopic measurement of rSO2 and the critical levels associated with neurologic impairement have not been determined. These cases provide 2 examples of rSO2 changes during HCA in the same aetiologic and operative procedure.

Key Words: *Hypothermic cardiac arrest, Near infrared spectroscopy*

Profoundly hypothermic total circulatory arrest has been commonly used for a variety of cardiac and complex vascular operations since at least 1959. However prolonged periods (>45 min) of hypothermic cardiac arrest (HCA) is associated with an incidence of adverse neurologic events (1,2). Brain is the target organ most sensitive to ischemic damage and the limiting factor in regard to the duration of circulatory arrest (CA) is cerebral tolerance (3). As a result a central objective of CA research is to define the 'safe' durations of CA and to develop techniques for monitoring this period (3,4).

Ouantitative EEG (QEEG), transcranial doppler ultrasound (TCD), jugular bulb oximetry and lately cerebral oximetry via near infrared spectroscopy (NIFR) are the techniques utilised for neurologic monitoring during deep hypothermia (5).

NIFR has several adventages over the aforementioned techniques for routine use during CPB. First, it is noninvasive, easier to use and less expensive. Second, it provides a regional estimate of cerebral tissue oxygen saturation (5, 6), rather than a global cranial measure. Third it does not require continuous cerebral perfusion so that it provides the only means of monitoring cerebral metabolic activity during deep hypothermic circulatory arrest. There are few data concerning the use of NIFR in cases of total circulatory arrest in humans and distinct results have been reported (7, 8). We are presenting here 2 cases of hypothermic circulatory arrest and the cerebrovascular saturation changes during the procedure.

CASE 1

58 yr old male patient (57 kg, 165 cm) with the diagnosis of renal cell carcinoma was scheduled for right radical nephrectomy and thrombectomy from inferior vena cava under hypothermic total circulatory arrest .

CT scanning and MR imaging of abdomen showed; a big heterogenous mass located in the right kidney extending to the renal hilus and a thrombus in the renal vein and inferior vena cava which extended to the right atrium.

Preoperative neurologic assessment of the patient was normal. On the day of surgery the patient was premedicated with meperidine 50 mg im. In the operation room heart rate monitoring by ECG, arterial O2 saturation by noninvasive pulse oximetry, systemic arterial pressure monitoring by right radial artery cannulation was started. Thiopental sodium 4 mg/kg, fen-

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Received: Jan 7, 1997 Accepted: June 24, 1997

tanyl 7mg/kg and vecuronium 0,1 mg/kg were administered for anesthetic induction. A central venous catheter (8.5 F) was inserted via right internal jugular vein and a 7.5 F Swan Ganz catheter was introduced in order to monitor pulmonary artery pressure, a urinary catheter, oesophagial and rectal temperature probes were also inserted. Anesthesia was maintained with isoflurane (1% vol.)/N2O (%50)in oxygen until radical nephrectomy was completed.

Following a 2 hr 15 min operation in the lateral decubitus position the patient was placed supine and anesthesia was further maintained with fentanyl infusion (total 30 mg/kg) and isoflurane (0.5-1%) /O2/air inhalation. Somanetics spectroscopy patch Invos 3100 (Somanetics Corp, Troy, Mich) was placed on the patients forehead approximately 1 cm above eyebrow. Initial cerebrovascular saturation was 80%. Median sternotomy was performed and systemic heparinization was achieved with a loading dose of (3 mg/kg) followed by boluses to maintain an activated clotting time of at least 400 seconds. Access for cardiopulmonary bypass was obtained via aorta, superior caval vein and right atrium. After cannulation, partial bypass was achieved. The patients rectal temperature was gradually decreased to 24°C by active cooling and spontaneous fibrillation was followed by asystole. At 20°C venous canulae were clamped and CPB was discontinued. Packs of ice were placed around the patients head during hypothermic circulatory arrest. Continuous monitoring of cerebral oxygen saturation was performed with spectroscopy. Initial measurement of cerebral oxygen saturation (rSO2) served as the patient's control value.

Spectroscopic measurements were taken before CPB, during cooling, circulatory arrest and reperfusion periods. A total of 34 measurements were recorded. 63% was the lowest recorded rSO2 throughout the whole procedure. Total hypothermic circulatory arrest time was 41 minutes. Rectal temperature was kept at 20°C during this period. During reperfusion the patients temperature was gradually increased to 33.4oC in a 53 minutes period. Warm blood cardioplegia was administered as a 'hot shot' at 27.3°C. Cardiac activity was seen at 33.4°C. CPB time was 70 min. 5 hr 40 min was the total operation time. Cerebral oxygen saturation and temperature changes in case 1 are presented in Figure 1. The patient was than transferred to the cardiovascular intensive care unit. He was weaned from mechanical ventilation on postoperative day 1. At the time of extubation he was orianted to time, place and person once reestablished via verbal communication. No deficit to motor or sensory function was observed. He was discharged from the hospital without any change in his neurologic status.

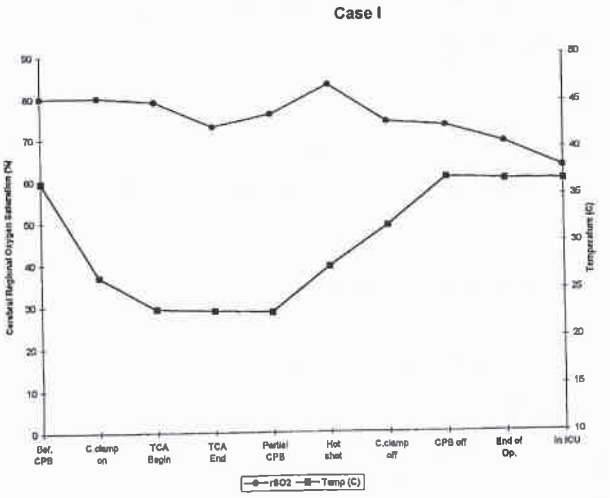

Fig. 1 . Cerebral oxygen saturation and temperature changes in case 1.

CASE 2

47 yr old male patient with the diagnosis of right renal tumoural mass and tumoural invasion of inferior vena cava was scheduled for right nephrectomy and removal of the thrombus from inferior vena cava by hypothermic total circulatory arrest.

Preoperative neurologic assessment did not reveal any abnormal finding. He was premedicated by diazepam 10 mg po. Following routine monitoring of pulse rate, arterial haemoglobin O2 saturation and invasive blood pressure anesthesia was induced by midazolam 0.1 mg/kg, thiopenthal sodium 5 mg/kg and atracurium 0.6 mg/kg. Anesthesia was further maintained by TIVA (fentanyl 30 mg/kg total and midazolam). Atracurium was the muscle relaxing agent during maintenance. An internal jugular catheher, urinary catheter and temperature probes (oesophageal and rectal) were also inserted before skin incision.

After right nephrectomy through a flank incision in the lateral decubitus position the patient was placed supine. Somanetics spectroscopy patch was placed on the patients forehead and initial measurement was obtained (64%). Median sternotomy was performed and following systemic heparinization access for CPB was achieved as in case 1.

250 mg thiopental sodium was administered iv before TCA as an approach to reduce cerebral metabolic rate. The patient was actively cooled to 18°C (rectal temp.). HCA time for removal of the thrombus from inferior vena cava was 28 min. Aortic cross clamp time was 95 min and total CPB time was 172 min. Cross clamp was removed at 30.3°C rectal and cardiac activity was seen at 32.3°C. The lowest recorded value of rSO2 was 54% during the procedure. Cerebral oxygen saturation and temperature changes in case 2 are presented in Figure 2. The patient was con-

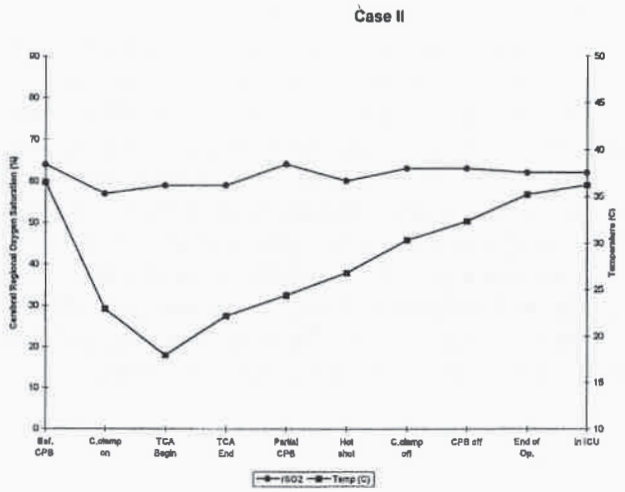

Fig. 2 . Cerebral oxygen saturation and temperature changes in case 2.

sistently hypotensive off CPB (mean arterial blood pressure ranged between 30-40 mmHg). An increase in pulmonary arterial pressures were also noted. Inotropic support was started and gradually increased, but there was no improvement in haemodynamic response. The patient's mean arterial pressure value remained below 44 mmHg in the 20 minutes period until his rectal temperature was increased from 32,3°C to 36,2°C. There was no significant decrease in cerebrovascular O2 saturation values. Blood-gas analysis in this period revealed hypoxemia and hypercarbia. Following skin closure he was transferred to the cardiovascular intensive care unit . The patient died 4 hours after the operation and the clinical situation was attributed to intraoperative pulmonary tumoural embolism.

DISCUSSION

Cerebral optical spectroscopy in the infrared light range has developed into a useful tool for physiologic monitoring of the brain. In 1977 Jobsis showed that near infrared light with a wavelenght of 700 to 1000 nm can penetrate through tissues. Infrared light (in this range) penetrates human tissue quite well; in the scalp, skull and cranial contents; it can penetrate several centimeters (9). This light can therefore pass through extracranial tissue into the brain and return to a sensor with valuable information concerning intracerebral attenuation of light (a noninvasive technique).

Near infrared light is differantially absorbed by oxygenated and deoxygenated blood and by cytochrome a,a3 (10). Haemoglobin has a peak of absorbance at 760 nm, but oxygenated haemoglobin (HbO2) absorbs at 900 nm. Oxidised cytochrome a,a3 absorbs at 780-870 nm and this disappears on reduction. The spectral analysis of transmitted light depends on the ratio of oxidised to reduced cytochrome a,a3. Hence, it shows the degree of oxygenation of the tissue being studied (9, 10).

The first clinical application of NIFR was in neonatal care and NIFR use in adults was first described in 1991 by Mc Cormick (9). The ability to measure cerebral oxygenation continuously and noninvasively has many applications including intensive care, neurosurgery, carotid surgery and during CPB. It is essentially important in clinical situations when cerebral hypoxia is a potential problem (9, 10). Cerebral ischemia and stroke remains a complication of coronary bypass surgery. Additionally neuropsychometric changes can be seen postoperatively. Peroperative use of NIFR can detect changes in cerebral perfusion and predict which patients are most at risk of postoperative neuropsychometric complications (11).

The absolute value of intracerebral oxygen saturation (rSO2) is about 70% in healthy adults. The change in rSO2 over time is the most useful measure of changes in cerebral perfusion. The manufacturers initially recommended positioning the sensors on the forehead. But increased cerebral penetration is possible by increasing the light source to detector seperation distance to 30 mm and 40 mm (12).

Although It is known that, deep levels of hypothermia (13 to 180C) reduce metabolism and offer some protection from ischemic organ damage upon initiation of cardiac arrest (CA) and complete absence of perfusion, ischemia will eventually occur as oxygen levels are depleted. Continuous spectroscopic measurement of cerebral haemoglobin oxygen saturation in 7 patients undergoing intracerebral aneurysm repair by HCA has been performed by Ausman et al (7) and circulatory arrest at 18oC was reported to be associated with significant progressive desaturation (rSO2<30% in 2 patients). In both of our cases no significant desaturation was noted during HCA. Our cases did not have any preoperative neurologic deterioration in contrast to the reported cases by Ausman et al. therefore it is difficult to state if any correlation should exist.

Rewarming from hypothermic cardiopulmonary bypass was associated with reduced rSO2 levels (<50% in 4 patients) and the reduction was atributed to microembolic insults and/or loss of cerebral autoregulation (13). In our case 1 rSO2 values were decreased compared to basal values during rewarming, but they remained above 60% in both cases.

In case 2 the patient was consistently hypotensive off CPB (MAP <44 mmHg with inotropic support), however rSO2 values were above 60% until the pa-

tient was transferred to the intensive care unit. We think that, further investigations are necessary especially in hypothermic and hypotensive patients before NIFR spectroscopy can be regarded as an efficient monitoring tool for cerebral function.

In conclusion, we have used continuous spectroscopic measurement of cerebral oxygen saturation to monitor adequacy of cerebral oxygenation during 2 cases of hypothermic cardiac arrest. There was no desaturation in both cases during HCA. Eventhough rSO2 values were decreased during rewarming in case 1 they remained above 60% in both cases. There was no neurologic impairement in this case. Case 2 was deliberately hypotensive after CPB however rSO2 levels did not show significant reduction. There are limited number of studies concerning continuous spectroscopic measurement of rSO2 in patients undergoing operative procerdures with HCA. Factors affecting rSO2 and the critical levels have not been clearly defined yet. Our cases provide two different examples of rSO2 changes during HCA in the same etiologic and operative procedure.

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IMMUNOGLOBULIN M-ENRICHED IMMUNGLOBULIN APPLICATION IN GRAM-NEGATIVE SEPSIS

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Işıl Gülay İltar** • Asuman Uysalel*** • Filiz Tüzüner***

SUMMARY

Gram negative sepsis is associatec with a mortality 20 to 70% in patients developing septic shock signs. Endotoxin is partly the reason of this high mortality. The endotoxin acts with activating intravascular coagulation, fibrinolysis, triggering the complement pathways, releasing cytokines and interleukins. Antibiotic therapy alone cannot reverse evolving gram-negative shock because of its delayed effect on endotoxine release through inhibition of bacterial growth and cell death. Neutralisation of endotoxin is the main target of the therapeutic interventions in these patients.

In this report we present a case of septic shock in which Immunoglobulin M (IgM) enriched Immunoglobulins treatment was successful.

Key Words: *Gram-negative sepsis, Immunoglobulin M enriched ımmunoglobulins*

Despite the development of new and effective antimicrobial agents and their early application in combination regimens, gram-negative sepsis is still associated with a mortality of 20 to 40% or even 40 to 75% in patients who develop clinical signs of septic shock (1,2).

This high death rate is partly attributed to endotoxin, the lipopolysaccharide (LPS) cell wall component of gram-negative bacteria. Endotoxin exerts its toxic effects through the activation of intravascular coagulation and fibrinolysis and through triggering the complement pathways and the release of cytokines such as tumor necrosis factor and interleukin 1 and interleukin 6 from activated mononuclear cells (1).

Antibiotic therapy alone cannot reverse evolving gram-negative septic shock because of its delayed effect on endotoxin release through inhibition of bacterial growth and cell death. Antibiotic damage of microorganisms may even temporarily increase circulating endotoxin levels and worsen the clinical course (2). For this reason, neutralisation of endotoxin and its main components has become a major target of therapeutic intervention in patients with gram-negative sepsis. For this purpose endotoxin-neutralizing antibody preparations are used (3,4,5).

In this report we present a case of septic shock in which Immunoglobulin M (IgM) enriched Immunoglobulins treatment was successful.

CASE REPORT

A 68 years old female patient was hospitalized in Intensive Care Unit because of respiratory insufficiency. The initial diagnosis was disseminmated infarction in mesensephalon and pontin area. After endotracheal entubation we started mechanical ventilation treatment. We started prophilactic second generation cephalosphorine. After 10 days the body temperature rised to 39^{o}C and pneumonia was diagnosed on chest X-ray. Smear from tracheal aspiration revealed abundant neutrophil leukocytes. On gram-negative culture of tracheal aspirates non-fermantative gram-negative bacillus was detected and blood culture revealed gram negative bacteriemia. A third generation Cephalosphorine, aminoglycoside and Teikoplanine combiñation was started. Hypotension (Systolic Arterial Pressure <90 mmHg, Systemic Vascular Resistance <400 dynes.sec.cm^{-5}) tachicardia (heart rate > 100 / seconds) and leukopenia (2500 /ml) were evident. After

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Received: June 9, 1997 Accepted: July 17, 1997

detecting the gram-negative septic shock clinical and laboratory signs we decided a course of IgM-enriched Immunoglobulins therapy. The treatment schedule was including 0.2 liter initial loading dose and 0.1 liter in every 6 hours for 72 hours. So that a total of 1.4 liters of immunoglobulins preparation was given (total 2 ml/ kg). At that moment epinephrine was given for hypotension according to the patient's status to increase systemic vascular resistance. Granulocyte colony stimulating factor (G-CSF) was applied to overcome neutropenia. On the second day of Immunoglobulin treatment arterial pressure and tachicardia were controlled and on the fourth day body temperature decreased around the level of 37° C. At that moment leukocyte count was 6700 / ml. After 10 days fever recurred (39° C) and the second course of Immunglobulin treatment was applied as the former schedule and on the second day of second course the body temperature was 37° C.

DISCUSSION

Since endotoxin is thought to be in the pathogenesis of gram-negative sepsis, immunoglobulins are used in the treatment to overcome circulating toxins (3,4,5). Although the mechanisms by which antibody preparations exert their potential beneficial effects are still not fully eludicated and altough it is still unclear how and whether antibodies which bind to the endotoxin cure in vitro can penetrate endotoxin side chains and occupy core determinants in vivo (6,7). Patients with low levels of antibodies against endotoxin core showed an increased frequency of febrile episodes and a higher mortality from gram-negative and endotoxin-positive septic shock (5). Experimental data strongly suggest a greater antitoxic and protective effect of polyclonal IgM rather than Immunogolbulin G (IgG) preparations (8,9). The unsuccessful results of the IgM treatment reports has been attributed to delayed onset of therapy and insufficient amount of these preparations (1,3). Following studies indicated that treatment with the IgM enriched immunoglobulin preparation provides highly protective antibodies by increasing the levels of IgM and IgG antibodies against endotoxin core (1,5,6,10). Furthermore, Ziegler et al. reported a reduction in mortality from gram-negative bacteremic shock by a human mononuclonal anti-lipid A IgM antibody (HA-1A) (3).

In the presented septic shock case IgM-enriched Immunoglobulin treatment was successful without side effects.

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THE ROLE OF EARLY DECOMPRESSION TO THE ORBITAL FRACTURES: A CASE REPORT

Funda Batay* • Ayhan Attar* • Ahmet Erdoğan**

SUMMARY

Serious injury to the optic nerve is an uncommon complication of the cranium fractures. Approximately 5% of all patients with head trauma manifest an injury to some portion of the visual system. Occasionally it is due to reversible changes. This case illustrated the importance of early decompression of the orbital fractures.

Key Words: *Optic nerve, Orbital fracture, Decompression*

Serious injury to the optic nerve is an uncommon complication of the cranium fractures. Approximately 5% of all patients with head trauma manifest an injury to some portion of the visual system. Occasionally it is due to reversible changes, such as contusion , edema or compression of the optic nerve. This case illustrated the importance of the early decompression of the orbital fractures (3,5).

Each optic nerve is approximately 50 mm in length , extending from the posterior aspect of the eye to the optic chiasm. Optic nerve is divided into four segments; intraocular, intraorbital, intracanalicular and intracranial. The intraocular portion of the optic nerve is about 1 mm in length with a diameter of 1.5 mm and exits the globe approximately 3 mm nasal to and slightly above the fovea. Surrounded by retina and choroid, the intraocular optic nerve is visible ophthalmoscopically as the optic disc. The intraorbital portion of the optic nerve extends from the posterior aspect of the globe to the optic canal, measuring 25 to 30 mm in length and 3 to 4 mm in diameter. This portion is covered by the dura mater, arachnoid,and pia mater of the brain. The intraorbital segment is making the optic nerve somewhat redundant and mobile within the orbit.It is surrounded by orbital fat and the extraocular muscles. The intracanalicular portion of the optic nerve measures about 10 mm in length 4 mm in diamater. In addition to the optic nerve, the canal contains the ophthalmic artery, postganglionic fibers of the carotid sympathetic plexus and extensions of the meningeal sheaths. In contrast to the intraorbital optic nerve the intracanalicular portion is fixed within the optic canal by the dura mater, which is tightly adherent to the bone within the optic canal. The intracranial segment of the optic nerve, an average of 10 mm in length, has a diameter of 4 to 7 mm. It is located above the diaphragma sella. Lateral to the optic nerve is the internal carotid artery. The frontal lobes of the brain lie above each optic nerve. The intracranial portion of the optic nerve terminates at the optic chiasm. The intracranial optic nerve receives small pial vessels originating from the internal carotid, the A1 segment of the anterior cerebral and the anterior communicating arteries (3,6).

The intracanalicular portion of the optic nerve is most frequently damaged as a consequence of closed head trauma. Occasionally, the intraocular segment is damaged, and ophthalmoscopic findings are then evident. In general, the intraorbital portion is spared because of its relative laxity within the orbit and the protection offered by the surrounding orbital fat and extraocular muscles, and this portion of the nerve is rarely involved because of its relative mobility within the head. Examination of the visual system after head trauma may be difficult or impossible. Nevertheless, every effort should be made to assess visual function using the following techniques; Visual acuity, pupillary reactivity, visual field testing, fundoscopic examination and sometimes visual evoked response (in comatose patient the VER provides some assessment of visual function). The early management of visual loss due to orbital fracture is controversial. Some authors recommend emergency optic nerve decompression; others advocate high dose steroid therapy alone.

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Received: Jan 17, 1997 Accepted: July 17, 1997

We present a case of complete unilateral loss of vision after head trauma with orbital fracture. The severity of trauma is not correlated with the severity of visual deficits. Because of the different morfological alterations the clinical , neurological and ophtalmological examination should be followed by standard CT scanning to evaluate intracranial hematomas and by CT scanning with thin slices of the optic nerves and the soft tissue of the orbit if there is indication (3,4,5,7).

CASE REPORT

A 40 year-old man was brought the emergency room after he was injured in a motor vehicle accident. On physical examination , there were multiple facial lacerations and a small subconjunctival hemorrhage on the left side . On neurological examination ; orientation and cooperation were intact , the left pupil was non reactive to direct light, reactive to indirect light, and the right pupil was also non reactive to indirect light. All the other cranial and spinal nerves examinations were normal . There was no vision on the left eye but the vision of right eye was normal .

Computed tomographic (CT) scans of the head and facial bones revealed a laterally displaced fracture of the lateral wall of the left maxillary sinus and fracture of the left orbital apex and major sphenoid wing without compressing the optic nerve. Additionally there was a fracture of the lateral wall of the sphenoidal sinus with no visible brain injury (Figure 1).

On the same date the patient underwent decompression of the left optic nerve via the pterional craniotomy and optic foraminatomy was performed. The compression of optic nerve by bony fragment, which was not detected in preoperative CT, was seen and removed at surgery. Preoperatively and postoperatively , the patient maintained on a course of dexamethasone sodium phosphate. Patient received 8 mg of dexametasone intravenously at the time of admission, during surgery and every 6 hours during the first 48 hours after surgery. His vision improved during early postoperative period. On his early vision examination , left eye was reactive to light. After two days the lefth eye could differentiate light and dark and four days later he was able to count fingers to the fifty centimeters.

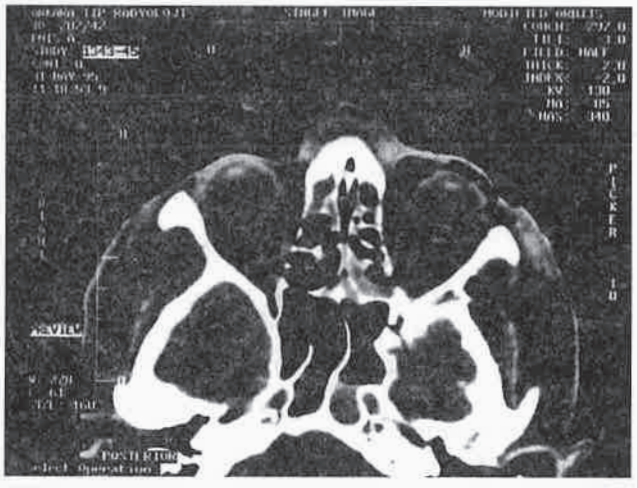

Fig. 1 .

DISCUSSION

The incidence of post-traumatic disturbances of vision varies in frequency in patients with head injuries. Some authors found that the severity of the ophthalmological lesions was independent of the severity of the trauma. Visual loss in patient with facial trauma may be due to hyphema, dislocated lens , retinal detachment, vitreous hemmorrhage, scleral rupture, retrobulber hematoma, optic nerve injury or occipital injury. An afferent pupillary defect with a normal funduscopic examination suggests injury to the optic nerve. Because Computed Tomography provides high resolution of soft tissue and bony structures as well as optimal views of the optic canal , which is essential for delineating the nature and location of injury in patients with traumatic visual loss (3,4).

The type of surgical decompression depends on the nature and extent of the injury causing the visual loss. Current techniques are craniotomy, orbitotomy, transethmoidal decompression, transantral-ethmoidal approach , and sphenoethmoidal approaches. Surgical decompression is usually decided on the basis of clinical findings. Important considerations in determining the need for and timing of surgery are the degree and progression of visual loss. Immediate and complete loss of vision associated with facial trauma is thought to carry a poor prognosis regardless of treatment. The radiological demonstration of a fracture of the optic foramen is not considered mandatory for exploration of the optic foramen. In fact, the patients who showed improvement of vision after surgery showed no fracture of the optic foramen on exploration. However , some patient with post traumatic blindness without optic foramen fractures on plain X-ray merits a CT scan. If this facility is not available , decompression of the optic nerve should be done on the basis of the clinical findings for exploration. Furthermore, it is belived that corticosteroids may reduce the traumatic edema and limit the severity of contusion necrosis of the optic nerve. The vasospasm that may accompany trauma may also be limited by high dose corticosteroids.

The prognosis is better in such cases which optic foramen is not fractured (1,2,5,8,9).

Although, the role of the orbital and optic nerve decompression in the management of patients with blindness following orbital trauma is controversial, according to our experiences , in a case of traumatic blindness , even if the plain X-rays do not reveal a fracture of the optic foramen , optic nerve decompression should still be performed on the basis of clinical presentations.

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PERFORATED VERMIFORM APPENDIX IN AN INGUINAL HERNIA

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Erdal Anadol*

SUMMARY

We present an unusual case of perforated appendix in an inguinal hernia sac. We considered the patient as having a strangulated small bowel hernia until the laparotomy revealed a perforated appendix in the sac. The possibility of appendicitis and its perforation within the sac should be kept in mind when there is a suggestive history, as was in our case. Exploring the groin before opening the abdominal cavity will be more appropriate, because of reducing peritoneal contamination in the presence of appendix perforation in the hernia sac.

Key Words: *Appendix Perforation, Inguinal Hernia*

Appendix perforation due to strangulation in an inguinal hernia sac is an unusual finding. The first report of an operation for hernia of the appendix that we have been able to find was by DeGarengrot in 1731 (1). The incidental finding of the normal appendix in the inguinal hernia sac is estimated to be %0.4 in adults. This incidence is higher in infants, as three times more common (2).In most of the reports acute appendicitis in a hernia sac occurs in past middle age as in our case (3).

CESE REPORT

36 years old male patient was admitted to the emergency service for high grade fever(39.3), tachycardia and abdominal pain. From the history we learned that abdominal pain had started from periumblical region and shifted to right lower quadrant and scrotum. Also he was suffering from constipation for three days. Physical examination revealed right lower quadrant tenderness, guarding and rebound tenderness, and also there was an irreducible right inguinal hernia which had a red and tender skin covering it. From the history we learned that he had a right inguinal hernia for three years. The plain abdominal X-ray film of the patient was normal, and the white cell count of the patient was 17600/mm3. Under these circumstances small bowel perforation due to strangulation in the inguinal hernia sac was suspected. Using general anesthesia we performed a high groin incision to gain access to the abdomen and hernia sac. Exploration of the abdomen showed a perforated appendix which was strangulated in the right inguinal hernia sac, there was some serous fluid in the abdomen and groin exploration through the internal inguinal ring revealed a sac filled with a purulent material. There were also significant inflammation of the vas deferens and testis that let us perform orchiectomy. Appendectomy, high suture ligation of the hernia sac and hernia repair by preperitoneal approach were performed. On the second day of operation we started oral feeding and he tolerated well. Except wound infection , which was treated appropriately the patient had no complication and discharged on the 7^{th} postoperative day. Pathologic examination revealed appendicitis and orchitis.

DISCUSSION

It has long been known that the appendix may be present in the contents of inguinal hernias, DeGarengrot reported the first case in the literature in 1731 (1). In the differential diagnosis of hernial appendicitis, the first condition to be considered is of course strangulated hernia. A careful history is essential in differentiating these two conditions (4). When making diagnosis we didn't pay attention to the history of the patient. His pain was started from periumblical region and shifted to the right lower quadrant and scrotum, simi-

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Received: Jan 15, 1997 Accepted: July 17, 1997

lar history as abdominal appendicitis. In many cases, the onset will be that typical of appendicitis, shifting pain from periumblical region to the right lower quadrant or hernia sac (4). This presentation must alert the physician about the presence of appendicitis in the hernia sac. But misdiagnose didn't let us wrong therapy. After this case we know think that hernia sac exploration will be more appropriate than laparotomy when you consider the possibility of perforated appendix in hernia sac, because periton contamination will be less if already not . Another but may be the most important thing is early recognition and treatment of these cases, otherwise unjustifiable events like orchiectomy may become evident.

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JOURNAL OF ANKARA MEDICAL SCHOOL Vol 19, No 3, 1997 177-179

FIBRODISPLASIA OSSIFICANS PROGRESSIVA: A CASE REPORT

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SUMMARY

Fibrodisplasia Ossificans Progressiva (FOP) is an extremely rare disorder of connective tissue. Progressive heterotophic ossifications of soft tissues may cause physical handicap. Diagnosis mainly depends on its characteristic physical and roentgenographical findings. There is no definite therapy in hand but early diagnosis, avoidance of precipitating factors, the patient and the family education and genetic counselling are the best therapeutic approaches.

Key Words: *Fibrodisplasia Ossificans Progressiva, Heterotophic Ossification*

Fibrodisplasia Ossificans Progressiva (FOP) also known as Myositis Ossificans Progressiva is an extremely rare disorder of connective tissue (1). It was first described by Patin in 1692 (2). The disease is determined as an autosomal dominant trait which has complete penetrance but variable expressivity and characterised by progressive disabling heterotophic ossifications of the tendons, ligaments, fascia, aponeurosis and connective tissue of muscles (1,2,3). Histologically lesions progress through an endocondral sequence of connective tissue proliferation, chondrogenesis, cartilage calsification and subsequent ossification (4). Some precipitating factors are mentioned as trauma, biopsy of the swelling, operations to excise ectopic bone, intramuscular injections, careless venipuncture and dental therapy (2). In this report a patient with FOP is presented.

CASE REPORT

A sixteen year old white female presented with a five-year history of firm soft tissue masses in the left side of her neck and periscapular area (Figure 1). Limitation of motion of her neck and shoulders, stiffness of back were also the presenting symptoms. Besides thoracal kyphoscoliosis, she had trigger finger deformity in her right fifth finger, toe deformities with short phalanx and hallux valgus (Figure 2). Her osseous nodules had been excised twice during the past 5 years. They were histologically diagnosed as calcifying fibroma and osteoma respectively. Her haematological, biochemical and bone turnover markers, tests for autoantibodis, immunoglobulins, complements, thyroid and adrenal gland function test were all in normal ranges. Electrocardiogram and echocardiogram revealed no abnormalities. Respiratory function tests showed a restrictive pattern. A high resolution karyotype analysis of cultured lymphocytes revealed a normal female 46, XX pattern. Roentgenograms of cervical spine showed small vertebral bodies with enlarged pedicules, fusion of arch and body between C2-C3. Third cervical vertebra anterolystesis and extensive ossification of the nuchal musculature were also noted (Figure 3). Anteroposterior roentgenographs of the chest showed extensive heterotopic ossification involving the area of ribs, scapula and clavicles (Figure 4). Ethydronate disodium (20mg/kg/day) was administered. Besides medical therapy, mild exercises for protection of range of motion of joints and muscle strengthening were applied. The use of adaptive and assistive devices to facilitate her daily living activities were encouraged and suggestions for environmental modifications were made. She was also trained about the avoidance of the precipitating factors. After a follow up period of six months, previous nodules did not disappear; but no new nodule formation was observed through this period.

DISCUSSION

We report here a case of FOP presenting with disabling ectopic ossifications in addition to characteris-

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Received: Apr 4, 1997 Accepted: July 17, 1997

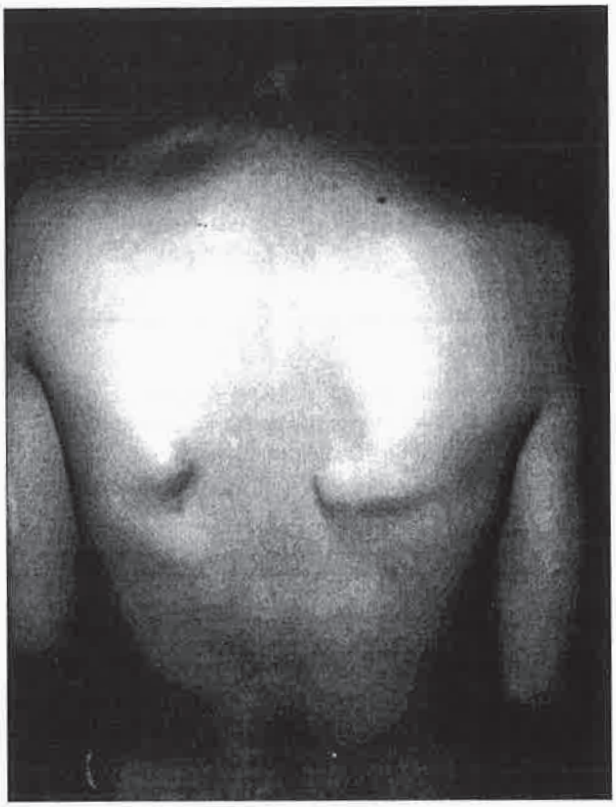

Fig. 1 . Photograph showing the osseous nodules at the neck and periscapular area.

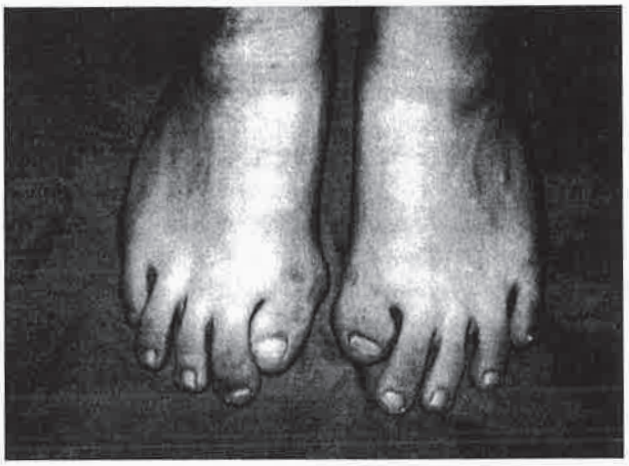

Fig. 2 . Photograph of toe deformities as short phalanxes and hallux valgus.

tic skeletal malformations. The patient can be accepted as fresh gene mutant as nobody with similar phenotype could be found in her pedigree. Old paternal ages have been reported to be responsible (1), but this was not the case in our patient as her father was 24 years old when she was born.

Characteristic skeletal malformations of FOP are as short monophalangic rigid big toes, reduction defects of all digits, short first metacarpals, fifth finger clinodactili, short, broad femoral necks, upper tibial exostosis and abnormalities in cervical vertebrae (1). Malformations tend to be bilateral and symmetrical except for the ectopic bone formations which are asymmetrical (5). The typical radiological findings reported up to now are soft tissue calcifications, widening of the metaphysis (especially at femoral necks giving the broad appearance), spur formation of the metaphysis, reduction defects of all digits and hallux valgus, shortening of proximal phalanx of the thumb and sometimes hypoplasia of the first metacarpus and a short metacarpus of the fifth finger causing clinodactili (5,6). In the cervical spine, nuchal ossifications, fusion of all neural arches, occipitoatlantal fusion and small vertebral bodies have been reported (3). Diagnosis mainly depends on early physical and radiological findings. There was no doubt that our patient was a case of FOP having finger deformity in her right fifth finger, toe deformities with short phalanx and hallux valgus, widespread heterotophic ossifications, small vertebral bodies with enlarged pedicules and extensive ossification of the nuchal musculature in cervical spine roentgenograms.

The progressions of the lesions were classified by Kaplan (4). During the first weeks pain, erythema, swelling, warmth and tenderness could be the only findings. After several weeks while swelling, pain and erythema decrease, induration increases. At the end of 12 weeks a hard, nontender lesion that is visible roentgenographically as a new area of calcification appears. TC 99m MDP Bone appears to be a very sensitive method of evaluation of active ossifications especially in the early, TC 99m MDP accumulates on newly forming by chemisorption (8). It can be used to monitor the extend of involvement with FOP and to detect areas of new activity prior to radiographic findings. Our patient's all lesions were considered as late lesions, therefore we did not find it necessary to have her bone scan done.

FOP causes physical handicap due to painful nodules which bridges and immobilises the joints rendering movement impossible (9,10). Early diagnosis and avoidance of the precipitating factors could halt the progress of the disease (9). In our patient restrictive lung disease might have occurred due to her kyphoscoliosis. Our patient was not in pain because of lack of early lesions, however she had quite physical disability as a result of the stiffness of her spine, shoulders and elbows.

Although different therapy modalities such as steroids, mineral binding agents (e.g. Ethylen-diaminetetraacetate), high doses of vitamin A, calcification blocking agents (e.g. Ethydronate disodium phosphate) probenecide, calcitonin, low calcium diet have been suggested, still a definite therapy could not be fo-

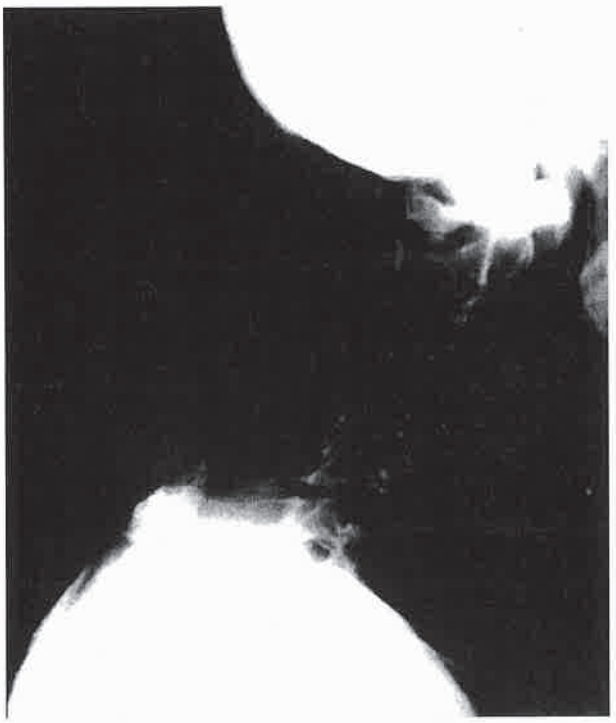

Fig. 3 . Roentgenograms of cervical spine showing small vertebral bodies with enlarged pedicules, fusion of arch and body between C2-C3, anterolystesis of third cervical vertebra and extensive ossification of the nuchal musculature.

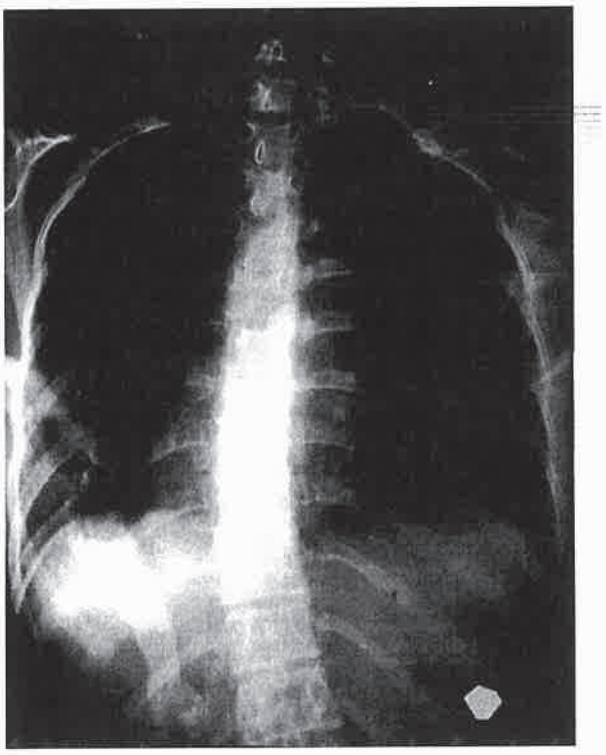

Fig. 4 . Anteroposterior roentgenographs of the chest showing extensive heterotophic ossification involving the area of ribs, scapula and clavicles.

und (1,2,5,6). There have been many reports for and against the use of ethydronate but it is still the most commonly used and suggested agent (1). Besides the use of adaptive and assistive devices for facilitating her daily activities, environmental modifications our patient was treated with disodium ethydronate (20mg/kg/day) for six months. No clinical or laboratory side effects were observed. All of her nodules were late lesions and none of them disappeared at the end of the trial. No new nodule formation was encouraging but since exacerbation and remissions could occur during the course of the disease, it is hard to say that this was due to therapeutic effect of ethydronate (5).

FOP has no definite effective treatment. Therefore besides some experimental approaches it is important that training of the patient and the family, genetic counselling and avoidance of the precipitating factors should not be forgotten (9,10). Rehabilitative approaches such as adaptive devices, environmental modifications are the mainstay of the therapy to reduce the handicap of the FOP patients.

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