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EPILEPSY: A NEW PATHOGENETIC APPROACH*

Aytaç Yiğit** • Güzin Özelçi Kavas*** • Ethem Akçıl*** • Pelin Arıbal Kocatürk***
Nermin Mutluer**

SUMMARY

The importance of reactive oxygen metabolites(ROM) in cerebral metabolism and cerebral pathology has become evident recently. In epilepsy pathogenesis ROM may contribute to the increase in neural excitability, and blood-brain barrier permeability. Because of the less efficient effect of glutathione peroxidase and catalase in the brain tissue, the only and primary intracellular antioxidant defense system is formed by superoxide dismutase(SOD).

Being a part of a series of studies on epilepsy, the alterations in the red cell SOD activity and plasma copper and zinc and the red cell copper and zinc concentrations and, plasma and the red cell magnesium concentrations were measured in patients with juvenile myoclonic epilepsy.

When compared with the control group; increased SOD activity, decreased plasma zinc concentration, increased red cell zinc concentration, decreased red cell magnesium concentration were found in epileptic patients.

Key Words: Juvenile myoclonic epilepsy, Reactive oxygen metabolites, Superoxide dismutase

Juvenile myoclonic epilepsy(JME), is a primary epilepsy characterized by abnormal neuronal function. This clinical condition reflects the intrinsic, non-progressive, and most probably hereditary cerebral disturbances. The only clinical sign of JME is single, rapid, recurrent, bilateral, synchronous shock-like jerks in the extremities, trunk, face and eyes, that are not associated with the loss of consciousness. The essential lesion in all epileptic events, is in the brain cortex including also the limbic cortex. Paroxysmal seizures in epilepsy are the result of neuronal abnormalities that continue in the cortex even during the remission (1). This neuronal disorder may occur as a result of cerebral ischemia-reperfusion, infection, trauma, metabolic disorders, increased intracranial pressure or brain tumors.

Recently, the role of reactive oxygen metabolites (ROM) and nitric oxide (NO) have been implicated in the pathogenesis of epilepsy. ROM and peroxynitrite which is the product of the reaction between NO with superoxide anion, have many damaging effects on neuronal function by increasing the permeability of blood-

brain barrier, inhibition of mitochondrial respiration and by disturbing synaptic transmission and ionic functions (2). The antioxidant defense system against the increased production of ROM and NO in brain tissue, is constituted from the antioxidant enzymes and the antioxidants as Vitamin E, Vitamin C, β -carotene. Because of the antioxidant potential of glutathione peroxidase (GPx) and catalase(CAT) in brain tissue is not so strong as in the other tissues the only effective and primary intracellular antioxidant defense system is formed by superoxide dismutase(SOD) (3).

This study was planned to evaluate the alterations in the red cell SOD activity and plasma and the red cell zinc (Zn) and copper (Cu) concentrations that are found in the structure of SOD, and in addition the changes in plasma and the red cell magnesium(Mg) concentrations in JME.

METHODS AND MATERIALS

Twenty JME patients, 8 female and 12 male with average age of 20 were included in the study whose diagnosis and follow-up had been made at the Neuro-

* This work was presented at the International Congress on Free Radicals in Health and Disease on 6th-10th September 1995, Istanbul, Turkey

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logy Department. Control group was consisted of 20 healthy individuals with average age of 22.

Blood samples were taken between 8.30-10.30 a.m., and the red cell SOD activity was measured by spectrophotometry(4) while plasma and the red cell Zn, Cu and Mg concentrations were determined by atomic absorption spectrophotometry (5).

The results had been confirmed statistically with Student's t test in the Department of Biostatistics, Ankara University Faculty of Medicine.

RESULTS

The results of the study are presented at the Table 1. When compared with the control group; increased red cell SOD activity, decreased plasma Zn concentration, increased red cell Zn concentration, decreased red cell Mg concentration were found in epileptic patients. Plasma Cu and red cell Zn concentrations were slightly increased and plasma Mg, red cell Cu concentrations were slightly decreased but these alterations were not significant statistically.

DISCUSSION

Many authors revealed the pathogenetic role of ROM in various central nervous system(CNS) pathologies(2,6,7,8). Within the brain there exists a variety of biochemical mechanisms which result in the production of ROM; these include the oxidation of catecholamines and dopamine catalysed by monoamine oxidase, prostaglandin metabolism. Fenton-iron catalysis, activation of macrophage-typed microglial cells and nitric oxide generation by brain endothelia and neurones, and its reaction with superoxide radical (6).

The only intracellular antioxidant defense system is performed by SOD in the brain tissue since there is a rich supply of these toxic radicals and low activities of GPx and CAT in the brain tissue. The CNS is highly

vulnerable to ROM mediated damage because of the high rate of oxidative metabolic activity, high concentration of readily oxidizable substrates as membrane lipid polyunsaturated fatty acids, and non-replicating capacity of neuronal cell and inability to repair the membrane (6).

In brain tissue ischemia-reperfusion, trauma, metabolic disorders, brain tumors and alterations in brain pressure leading to neuronal abnormality may alter the impulse threshold. Ischemia induces the membrane depolarization and causes the release of excitatory neurotransmitter as glutamate. Glutamate is bound by two ionotropic receptors that can be distinctively activated by either N-methyl-D-aspartate(NMDA) or α -amino-3-hydroxy-5-methyl-4-isoxazole propionic acid(AMPA). Mg-mediated blokage on NMDA receptors is disappeared by depolarization and by NMDA receptor activation, slow calcium channels are opened and intracellular calcium concentration increases ; on the other hand, AMPA receptor activation opens sodium channels and allows the increase of intracellular sodium concentration. Increased intracellular sodium concentration prevents the efflux of calcium from the cell, there by again increasing the calcium concentration intracellularly, result in the cytotoxic effects (2,3). During ischemia in brain, ATP concentration decreases because of the disturbed oxidative metabolism and this causes an increase of intracellular calcium concentration leading to lipolysis and increased metabolism of free fatty acids and increased nitric oxide synthase activity, hence these events accelerate arachidonic acid metabolism and production of nitric oxide (3).

Both the increased production of ROM due to the increased arachidonic acid metabolism and the increased production of NO accelerates the lipid peroxidation resulting in the structural and functional disorders in neurons. It has been shown that similar changes are

Table 1: Superoxide Dismutase Activity and Trace Element Concentrations of the Patients with Juvenile Myoclonic Epilepsy

Parameter	Control Group n=20 $\bar{X}\pm SD$	Epileptic Group n=20 $\bar{X}\pm SD$	Statistical Analysis
The red cell SOD activity (U/g Hb)	3202 \pm 373	4543 \pm 514	p<0.001
Plasma Cu concentration (μ g/dl)	108.25 \pm 17.93	115.00 \pm 21.14	p>0.05
The red cell Cu concentration (μ g/ml)	0.67 \pm 0.08	0.56 \pm 0.25	p>0.05
Plasma Zn concentration (μ g/dl)	125.30 \pm 28.52	107.65 \pm 22.18	p<0.05
The red cell Zn concentration (μ g/ml)	8.45 \pm 1.21	9.54 \pm 1.98	p<0.05
Plasma Mg concentration (mg/dl)	2.51 \pm 0.30	2.41 \pm 0.23	p>0.05
The red cell Mg concentration (μ g/ml)	52.79 \pm 7.40	47.82 \pm 5.62	p<0.05

seen in the red cell membrane (9). Indeed, the significant increase in the red cell SOD activity in our study indicated that there is an oxidative effect also on the red cells as seen on neurones in epilepsy.

In addition, superoxide anion reacts with NO to form peroxynitrite (ONOO⁻) and peroxynitrite forms more toxic agents like hydroxyl radical(OH[•]) and nitrogen dioxide (NO₂) (10).

In our study we found very significant increase in SOD activity suggesting increased ROM production in JME. The red cell SOD activity that we choosed as an indicator of intracellular antioxidant defense system, was found to be increased very significantly. Trace element, zinc, that found in the structure of SOD and responsible from it's stability, was found in low concentration in plasma and high in the red cell, showing the increased uptake of Zn into the cell to provide the

increased utilization for SOD stability. The slight decrease of plasma Mg concentration that was not statistically significant, but on the other hand marked decrease in the red cell Mg concentration which was statistically significant, may be correlated with the alteration of the membrane potential threshold. The decrease in the intracellular Mg concentration causes disturbances in Na⁺-K⁺-ATP ase function and membrane stability and this in turn results in the neuronal hyperexcitability (11,12). Additionally, the decrease in intracellular Mg concentration by leading to the increase in intracellular calcium concentration may contribute to the epilepsy pathogenesis (12,13,14).

In conclusion, our study showed the importance of ROM and make consider the important role of Mg ion in the epilepsy pathogenesis. Our findings correlate with the literature data.

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SERUM PLATELET DERIVED GROWTH FACTOR LEVELS IN PATIENTS WITH LUPUS NEPHRITIS

Ali İnal* • Göksal Keskin* • Murat Turgay* • Gülay Kınıklı*

SUMMARY

Platelet derived growth factor (PDGF) is initially isolated from platelets as a potent mitogenic factor. The role of PDGF in pathogenesis of many disease has been investigated. We investigated serum levels of PDGF in 55 SLE patients (45 female, 10 male, mean age of 33.6, 45 active and 10 inactive) and 25 healthy persons (16 female and 9 male, mean age of 31.8). Twenty five SLE patients had renal involvement. Histopatological diagnosis and, chronicity and activity indices were assessed.

There were no difference in serum PDGF levels between patients with active SLE (1110.7 ± 618.8 pg/ml) and inactive SLE (1498 ± 505.8 pg/ml) and controls (1210 ± 399.7 pg/ml). There were no difference concerning serum PDGF levels in the patients with renal involvement (913 ± 528.4 pg/ml) comparing with control group and patients without renal involvement (1366 ± 632.6 pg/ml).

There were no difference between the groups with activity index 0-3 (1068 ± 458.4 pg/ml) and 4-8 (985 ± 548.5 pg/ml), and between the groups with chronicity index 0 (1102.6 ± 286.2 pg/ml) and 1 (1021.6 ± 216.1 pg/ml) and control group ($P > 0.05$, $P > 0.05$ respectively). Serum PDGF levels were significantly low in the groups with activity index 9-12 (579 ± 224.5 pg/ml) and 13-16 (449.7 ± 261.3 pg/ml), and in the groups with chronicity index 2 (529 ± 118.5 pg/ml), 3 (477 ± 148.5 pg/ml) and 4-6 (380 ± 99.4 pg/ml) compared with control group ($P < 0.05$, $P < 0.05$, $P < 0.05$, $P < 0.05$, $P < 0.05$ respectively).

The results show that serum levels of PDGF are low in patients with activity and high chronicity indices.

Key Words: Systemic lupus erythematosus, Nephritis, Platelet derived growth factor

Platelet derived growth factor (PDGF) is a disulfide-linked dimer with a molecular weight 30kda. PDGF consists of two peptide chains as A and B. These chains are the products of distinct genes and PDGF can be either homodimeric (PDGF AA and PDGF BB) or heterodimeric (PDGF AB) (1)

PDGF is initially isolated from platelets as a potent mitogenic factor. Recently, it has been found that PDGF is produced by many cells, including arterial endothelial cells, activated monocyte/macrophages, cytotrophoblasts, neoplastic cells, smooth muscle cells and stimulated fibroblasts (2-8).

The potent activity of PDGF as a mitogen, the reports that many transformed cells and tumor cells express some form of PDGF and PDGF-related molecules suggest that PDGF has an autocrine role (9). The varied types of biological activities reported for PDGF suggest possible in vivo roles in normal and pathological

processes (10, 11). Other functions of PDGF include its ability to stimulate protein synthesis, phospholipid and cholesterol esters, and prostaglandins (12). There is a body of evidence to suggest that PDGF derived from macrophages can act as a chemotactic and growth stimulatory agent for smooth muscle cells, resulting in the myointimal thickening characteristic of atherosclerotic lesions (13).

Recent studies have provided evidence that PDGF β -chain has a important role both in experimental and human nephritis (14). Immunohistochemical evidence for participation of PDGF in human disease has been provided by studies which have localized PDGF to mesangial areas in IgA nephropathy and other mesangial proliferative glomerulonephritis (14-16). Some investigators have already offered hypotheses that link PDGF to renal interstitial fibrogenesis (14, 17, 18).

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Despite recent impressive improvements in patient survival, renal disease secondary to systemic lupus erythematosus (SLE) is still associated with high morbidity and mortality rates. The characteristic immunologic abnormality in the pathogenesis of SLE is uncontrolled production of autoantibodies, platelet function, fibrinolysis and endothelial cell functions. Chronic platelet activation, platelet hyperaggregability, and intraglomerular platelet antigens are frequent in lupus nephritis (19, 20).

Since chronic release of PDGF might lead to the proliferative vascular lesion seen in lupus nephritis we decided to investigate in serum samples from patients with lupus nephritis. In this study, we researched serum PDGF levels, and its correlation with disease activity and histopathological evaluation in patients with lupus nephritis.

MATERIALS AND METHODS

The serum samples were obtained from patients with SLE and from 25 healthy controls (16 women and 9 men; age range: 20-45 years, median 31.8 years) at Ankara University, Faculty of Medicine, Department of Immunology. Fifty-five SLE patients (45 female, 10 male) were studied. Each patient satisfied the American Rheumatism Association (ARA) clinical criteria for the classification of SLE (21). The patients, mean age was 33.6 years (range: 14-60). Patients were initially classified as having active and inactive disease. The disease activity was based on SLEDAI (22). Forty-five patients, between ages 14-55 (mean age: 33.2) were active and 10 patients, between ages 17-60 (mean age: 33.8) were inactive. In all patients, mean disease duration was 3.2 ± 1.5 years.

We assessed renal involvement with renal biopsy and urine analysis. The patients with lupus nephritis were considered to have active nephritis by the presence of abnormal urinary sediment, including hematuria and/or cellular casts and abnormal proteinuria (>0.5 gr/day) and deteriorating renal function. The clinical and laboratory assessments were performed at the same time as the renal biopsies obtained and we had also taken serum samples. The study design admission criteria and definitions for clinical, laboratory and biopsy variables were the subject of an earlier report (23). All the active patients with renal involvement had hypocomplementemia (C3 and C4) and high titers of antibody to native DNA. Among the 55 SLE patients, 25 had renal involvement. Fourteen SLE pati-

ents with renal involvement, proteinuria was 0.5-1gr/day, in 6 was 1-4 gr/day, in 5 was 4.5-7 gr/day. In other patients with SLE, there were no manifestations related to renal involvement, so renal biopsy was not performed. The majority of renal biopsies demonstrated diffuse proliferative glomerulonephritis (=GN) (n=12). Six patients had membranous GN, 4 had mesangial GN, and 3 had focal proliferative GN.

Biopsies were also classified according to the presence of chronic renal lesions (glomerular sclerosis, interstitial fibrosis, fibrous crescents, tubular atrophy) and active renal lesions (glomerular hypercellularity, leukocyte exudation, karyorrhexis/fibrinoid necrosis, cellular crescents, hyaline thrombi, tubulointerstitial inflammation) as defined by the indices reported by Austin et al (24). Individual lesions were scored 0 to 3+ (absent, mild, moderate, severe).

Indices of activity and chronicity in patients with renal involvement were grouped according to criteria of Esdaile et al (23). The prevalence of indices of activity and chronicity are shown in Table 1 and Table 2.

All inactive patients had only received 250 mg/day chloroquine at the same time of study. Among the 25 patients with renal involvement, 13 were not on therapy. Other 12 patients were diagnosed before and during the study they were received low dose prednisone (<15 mg/day). Other active SLE patients without renal involvement had received 10-20 mg/day prednisone.

The serum samples are collected in pre-chilled serum separator tubes. Later we centrifuged the serum samples at 4°C, and stored them at -20°C until analysis. Platelet derived growth factor in serum samples was determined by sandwich enzyme immunoassay using Quantikine-Human PDGF-AB immunoassay kit purchased from Abingdon, UK.

Statistical analysis of the results was performed using student's t test and Mann-Whitney-U test.

RESULTS

Evaluation of symptoms according to the activation of disease, in active patients are shown in Table 3. In active group the most common symptom was arthralgia (82.2 %) and the least common was neurological involvement (11 %). There were no age and sex difference between the patients and control group. There were no correlation between serum PDGF levels and age, sex in the patients and controls. The mean platelet derived growth factor levels in serum samp-

Table 1. The prevalence of indices of activity and mean platelet derived growth factor levels in serum samples in patients with renal involvement.

Patients (n)	%	Activity index	Serum PDGF levels (pg/ml \pm SD)
6	24	0-3	1068.0 \pm 458.4
9	36	4-8	985.0 \pm 548.5
7	28	9-12	579.0 \pm 224.5
3	12	13-16	449.7 \pm 261.3

*Serum PDGF levels were low in patients with activity indices 9-12 and 13-16 compared with 0-3, 4-8 and control group (all $p < 0.05$).

Table 2. The prevalence of indices of chronicity and mean platelet derived growth factor levels in serum samples in patients with renal involvement.

Patients (n)	%	Chronicity index	Serum PDGF levels (pg/ml \pm SD)
10	40	0	1102.6 \pm 286.2
4	16	1	1021.2 \pm 216.1
2	8	2	529.0 \pm 118.5
4	16	3	477.0 \pm 148.4
5	20	4-6	380.0 \pm 99.4

*Serum PDGF levels were low in patients with chronicity indices 0 and 1 compared with 2, 3 and 4-6 (all $p < 0.05$).

Table 3. Symptoms in active SLE patients

Symptoms	Patients (n=45)	%
Arthralgia/arthritis	37	82
Skin lesion	32	71
Oral ulcers	30	67
Renal involvement	25	56
Serositis	21	47
Hematological involvement	10	22
Neurological involvement	5	11

les of patients with renal involvement and control group are shown Figure 1. The mean platelet derived growth factor levels in serum samples of patients according to activity and chronicity index are shown in Table 1 and Table 2.

There were no significant difference serum PDGF levels between patients with active SLE (1110.7 \pm 618.8 pg/ml) and inactive SLE (1498 \pm 505.8 pg/ml) and controls ($P > 0,05$). Although, serum PDGF levels were low in patients with renal involvement (913 \pm 528.4 pg/ml) compared to control group (1210 \pm 399.7 pg/ml) and patients without renal involvement (1366 \pm 632.6 pg/ml), it had no statistical significance ($P > 0.05$, $P > 0.05$ respectively).

Comparison of serum PDGF levels according to the activity and chronicity indices: There was no difference between the groups with activity index 0-3 (1068 \pm 458.4 pg/ml) and 4-8 (985 \pm 548.5 pg/ml), and

between the groups with chronicity index 0 (1102.6 \pm 286.2 pg/ml) and 1 (1021.2 \pm 216.1 pg/ml) and control group ($P > 0.05$, $P > 0.05$ respectively). Serum PDGF levels were significantly low in the groups with activity index 9-12 (579 \pm 224.5 pg/ml) and 13-16 (449.7 \pm 261.3 pg/ml), and in the groups with chronicity index 2 (529 \pm 118.5 pg/ml), 3 (477 \pm 148.5 pg/ml) and 4-6 (380 \pm 99.4 pg/ml) compared with control group ($P < 0.05$, $P < 0.05$, $P < 0.05$, $P < 0.05$, $P < 0.05$ respectively).

DISCUSSION

Platelet derived growth factor is a potent mitogen for connective tissue cells, including dermal fibroblast, glial cells, arterial smooth muscle cells, glomerular mesangial cells (25) and some epithelial and endothelial cells (26-29) and it also shows a strong chemoattractant property for human monocytes, neutrophils and fibroblasts and for smooth muscle cells (30, 31).

Serum from some patients with scleroderma contains increased levels of mitogenic activity for fibroblasts; this activity can be reduced if the patients are treated with pharmacological agents that decrease platelet activity. Immunohistochemical studies have demonstrated PDGF in scleroderma skin lesion, especially associated with mononuclear infiltrates and the endothelial lining of capillaries (32). The detection of

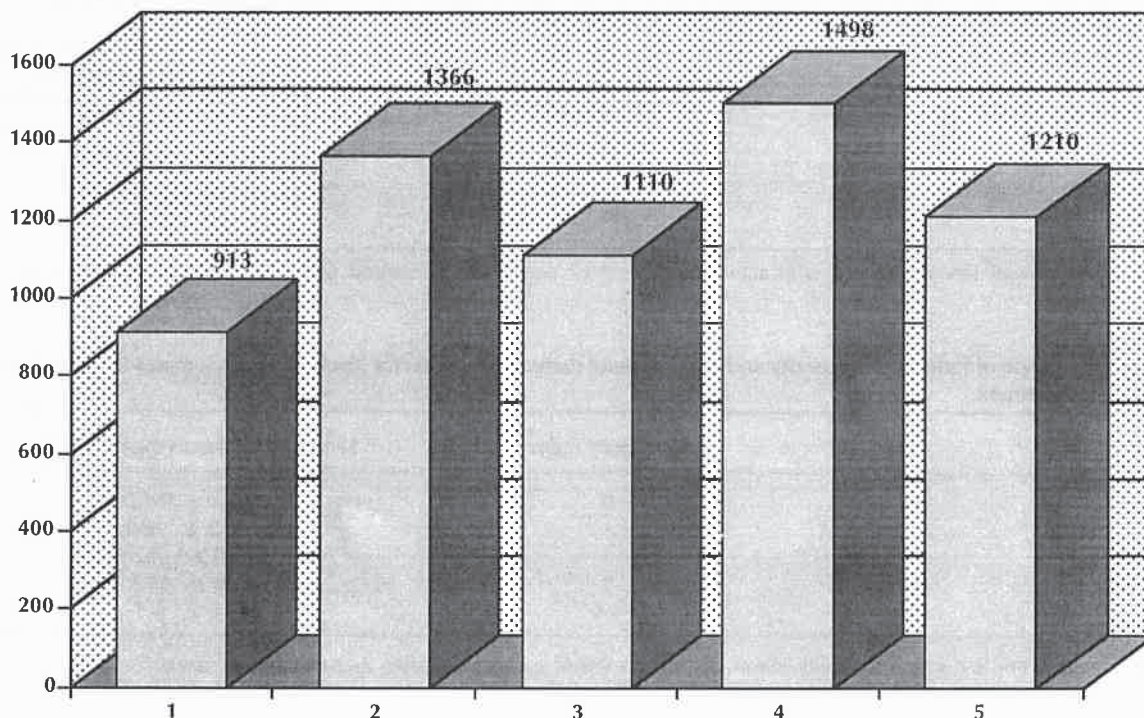


Fig. 1: Mean platelet derived growth factor levels in serum samples of patients and control group: 1. Patients with renal involvement, 2. Patients with no renal involvement, 3. Active SLE patients, 4. Inactive SLE patients, 5. Control group. There were no significant difference between all groups.

PDGF at these sites suggests that PDGF release from platelets at sites of vascular injury may be an important step in the pathophysiology of scleroderma (32, 33), but plasma PDGF concentrations in scleroderma patients are discrepancy (33, 34).

In chronic synovitis, PDGF receptors are increased in the synovium (1). Chronically inflamed joints of RA patients are characterized by massive tumorlike synovial hyperplasia (35). Recent studies have shown that PDGF and PDGF-like factors are present in serum and rheumatoid synovia and suggest that the PDGF and PDGF-like factors detected are biologically active and contribute to the synovia pathology of rheumatoid arthritis (36).

According to our knowledge, there is not enough information about serum PDGF concentration levels in SLE patients. In our study, we evaluated both serum PDGF levels in patients with and without renal involvement, and in active and inactive patients the relationship between clinic and histopathologic features.

There was no difference between the mean PDGF concentration in 45 active SLE patients compared with inactive SLE patients and control group ($P > 0.05$). Evaluation of renal biopsies in lupus nephritis, with activity and chronicity indices are important for prognosis and therapy. In patients with activity indices 9-12 and 13-16, serum PDGF levels were low compared with patients with activity indices of 0-3 and 4-8 ($P < 0.05$, $P < 0.05$, $P < 0.05$ respectively). This is really an unexpected result. According to our theoretic knowledge, it should be just opposite. PDGF that did not bind locally would then be rapidly inactivated by binding to the plasma components and cleared. In the group with low activity indices, we couldn't explain the reason of high levels of serum PDGF, because there was no pathological condition, like vasculitis, that could effect thrombocyte activation. In addition, there was no difference in the number of thrombocytes in patients with low activity indices and in patients with high activity indices. We evaluated the relation between

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CRANIOPHARYNGIOMA AND POTENTIAL ENDOCRINE SEQUELAE IN CHILDHOOD

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SUMMARY

The postoperative course of 16 children undergoing surgery for craniopharyngioma (CRA) was reviewed for neuroendocrine dysfunctions. All had an attempt at radical or partial surgical resection of the tumor with no radio or chemotherapy. Antropometric measurements, pubertal staging, neuroendocrine evaluation (GH provocative testing, Thyroid function tests, HPA axis activity, salt-water balance, serum prolactine values) were made for assessment of endocrine course.

Hypopituitarism with multiple hormone deficiency in vary combination was found in all of the patients (100 %). We observed GH-deficiency 81.25%, hypothalamo-pituitary-adrenal axis impairment 75%, hypophysial hypothyroidism 68.75%, complete or partial central diabetes insipidus 56.25%, short stature 56.25%, obesity 50%, hyperprolactinemia 18.75%, transient hypodyspic hypernatremic syndrome 18.75%, complete puberty precocious 12.5% of patients. None of them had isolated hormone deficiency. Eleven of 16 patients had deficits of four or more neuroendocrine dysfunction. Six out of 13 GH-deficient children showed normal growth pattern (normally growing GH-deficient children). Obesity was more prominent in normally grewed patients then the patients with short stature.

Our data showed that endocrine sequelae is an inevitable result of CRA. When possible full evaluation of pituitary function should be performed ; the minimum preoperative evaluation must include testing for and treatment of ACTH-adrenal insufficiency and diabetes insipidus, hypodipsia-hypernatremia associations.

Key Words. Childhood, Craniopharyngioma, Endocrine sequelae

Craniopharyngioma (CRA) is most common childhood tumor to involve the hypothalamus and pituitary region (1-3). They are benign but aggressive and recurrent neoplasms. The sequel of CRA are numerous. The growth of the tumor in relation to the adjacent anatomical structures significantly influences both the mode of presentation and the neuroendocrine complications. Although endocrine disturbances can be found in a great percentage of the patients at presentation, only a minority of subjects seek medical attention for an endocrine-related complaint (4-7). Following complete surgical resection of a CRA, combined anterior and posterior pituitary dysfunction were became clinically evident (8-10).

We evaluated 16 children admitted with diagnosis of CRA for neuroendocrine dysfunction in the post operative period.

PATIENTS AND METHODS

Postoperatively diagnostic studies of endocrine dysfunction were performed in 16 patients (9 girls-7 boys) with CRA, aged 3.9 to 14 years (mean age 8). All had attempt at radical or partial resection of the tumor with no radio or chemotherapy. In their history of CRA headache, nausea, vomiting, visual loss, diplegia, obesity, diabetes insipidus and convulsions were presenting symptoms.

Patients workup in postoperative period included, antropometric measurement (height, height SDS for chronological age, body weight, weight, length index); pubertal staging (Tanner method) ; analysis of thyroid function tests (tT3, tT4, FT3, FT4, basal TSH); growth hormone response to phamacological stimulation (L-Dopa and/or insulin); pituitary adrenal axis activity (presence or abcence of low morning cortisol without

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elevation of ACTH) ; salt-water balance within body (urinary volume, density, osmolarity and DDAVP tests) and serum prolactine values. The values for the samples were determined on the basis of standard radioimmun assay kits. Growth hormone reserve was considered normal when GH concentrations exceeds 10 ng/ml. Frequency of neuroendocrine disturbances was determined. Correlation between the degree of the obesity (WLI) and the growth retardation (HSDS) was also evaluated.

RESULTS

Table 1 presents detailed clinical and hormonal features of patients with CRA. Approximately 81.25 % of patients had optic atrophy. Hypopituitarism with multiple hormone deficiency in vary combination (GH, TSH, ACTH, ADH) was found in all of the patients. The frequency of endocrine disturbances are given in Table 2.

Growth hormone deficiency, short stature and obesity were observed in 81.25 %, 56.25 % and 50 % of patients, respectively. Figure 1 presents the correlation between degree of growth retardation and obesity. Body weight length index (WLI) was 131,62±34,17 in patients without growth retardation (HSDS -1.45±0.56), whereas in short statured patients (HSDS-3.7± 1.09) WLI was 114.25±25.73 (Table 3).

Central hypothyroidism with low thyroxine (5.8±2mg/dl) without elevated TSH (1.58±0.6mU/ml) was observed at 68.75 % of patients. Low basal cortisol values (<10mg/dl) without elevated ACTH (26.04±27pg/ml) levels was determined in 75 % of them.

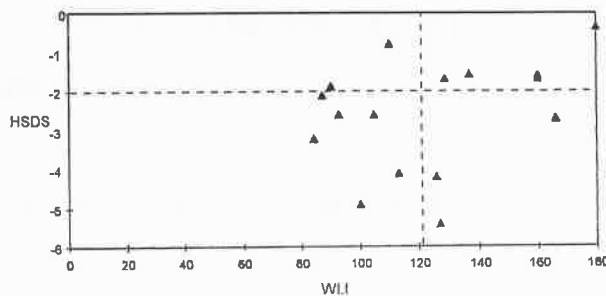


Fig. 1: Correlation between WLI and HSDS of CRA patients.

Partial or complete central diabetes insipidus and hypodipsic hypernatremic syndrome were diagnosed in 56.25 % and 12.5 % of patients, respectively.

Central puberty precocious (n=1), transient anorexia (n=3), hyperprolactinemia (n=2) were other important neuroendocrine dysfunction in a few number of our patients with CRA.

DISCUSSION

Craniopharyngioma generally develops either in the suprasellar region or in both suprasellar and intrasellar region (2-4). Craniopharyngioma of childhood is a different entity than the tumor found in adulthood. Microscopically adamantinomatous tissue is found in children whereas a squamous epithelial origin is more predominant in adults (1). Partial resection is of little benefit in children because adamantinomatous tumors grow fast rate. Following complete surgical resection of CRA combined anterior and posterior pituitary deficiency is present in majority of patients (8,9). Surgery product some additional disturbances in endocrine

Table 1: Clinical and Hormonal Features of Patients with CRA In the Postoperative Period

No	Patient Name	Age at CRA years	Age at admission years	Puberty Stage	Obesity WLI (122,9±29,6)	Optic Atrophy	Diabetes Insipidus	Short Stature (Hsds)	GHD (GH peak ng/ml)	Secondary Hypothyroidism (T4 µg/dl - TSH mU/L)	HPA-axis Impairment (cortisol µg/dl - ACTH pg/ml)	Puberty Precocious Hypertremic Syndrome	Transient Hypodipsic	Hyper prolactinemia	Transient Anorexia
1	MY	8,7	8,8	P1	+(137)	+	+	- (- 1,57)	+(0,22)	+(5,9-0,01)	+(0,32-12,9)	+	-	-	-
2	EYT	13	13	P1	+(160)	+	+	- (- 1,6)	+(0,55)	+(4,8-0,1)	+(1,4-14,4)	-	-	-	-
3	GT	3,9	7	P4	+(160)	+	-	- (- 1,6)	- (10)	- (7,0-1,9)	+(5,8-46,0)	+	-	-	-
4	MM	5	5	P1	- (90)	+	-	- (- 1,9)	+(3,1)	- (13,1-1,4)	+(8,0-10,1)	-	-	+	-
5	MA	6	7	P1	- (84)	+	+	+(-3,2)	+(3,7)	- (6-1,9)	- (8,0-25,0)	-	-	-	-
6	HK	8	8,5	P1	+(129)	-	-	- (- 1,7)	+(1,7)	+(5,6-0,35)	- (22,3-8,0)	-	-	+	-
7	AK	13	13	P1	- (105)	+	+	+(- 2,6)	- (> 10)	+(4,8-1,7)	+(6,1-6,0)	-	-	-	-
8	FD	11,6	13,7	P1	+(166)	+	-	+(-2,7)	+(5,4)	+(3,0-0,2)	+(0,9-18,3)	-	-	-	+
9	MA	9	9,1	P1	+(126)	+	+	+(-4,2)	+(0,9)	+(4,2-0,1)	- (11,3-27,0)	-	+	-	+
10	NK	6,9	7,5	P1	- (93)	+	+	+(-2,6)	+(1,1)	+(4,3-3,0)	+(2,1-25,5)	-	-	-	-
11	SA	4,2	4,5	P1	- (110)	+	+	- (-0,8)	+(5,4)	+(2,8-2,0)	+(3,9-1,3)	-	-	-	-
12	ET	5,7	5,8	P1	+(180)	+	-	- (-0,3)	+(6,2)	+(4,6-4,2)	+(1,5-49,9)	-	+	-	+
13	HO	13,5	14	P1	- (100)	+	-	+(-4,9)	+(0,7)	- (7,6-5,3)	+(8,0-26)	-	-	-	-
14	GK	9	9,2	P1	+(127)	-	+	+(-5,4)	+(2,1)	- (8,0-2,2)	- (23,7-118,0)	-	-	-	-
15	EO	11,3	12,1	P1	- (113)	-	-	+(-4,1)	+(5,7)	+(3,8-3,2)	+(6,6-20,3)	-	-	+	-
16	BO	6	6,4	P1	- (87)	+	-	+(-2,1)	- (13)	- (9,0-1,9)	- (23,8 - ?)	+	-	-	-

Table 2: The Frequency of Endocrine Disturbances in CRA postoperatively.

Endocrine Disturbances	Patients Numbers	Frequency
Growth Hormone Deficiency	13/16	81,25
Hypothalamo-Pituitary-Adrenal-Axis Impairment	12/16	75
Secondary Hypothyroidism	11/16	68,75
Short Stature	9/16	56,25
Central Diabetes Insipidus	9/16	56,25
Obesity	8/16	50
Transient Anorexia	3/16	18,75
Hyperprolactinemia	3/16	18,75
Transient Hypodyspic Hypernatremic Syndrome	2/16	12,75
Complete Puberty Precocious	2/16	12,75
Delayed Puberty	1/16	6,25

Table 3: Comparison of the degree of obesity (WLI) in GH-deficient CRA children with or without short stature (n=13)

	HSDS	WLI	Peak GH-response to L-Dopa(ng/ml)
Patient with short stature (n=7)	-3.71±1.09	114.25±25.7	3.22±0.51
Patient without short stature (n=6)	-1.45±0.5	131.62±34.17	5.02±4
Significance	S	S	NS

function, especially for the incidence of diabetes insipidus which was doubled (6).

The presenting preoperative endocrinological abnormalities were reviewed in Imura et al (7). Incidence of neuroendocrine disturbances reported by them were ; hypopituitarism 91% (multiple hormone deficiency 83 %, isolated hormone deficiency 9 %, pituitary dwarfism 24 %), diabetes insipidus 41 %, obesity 42 %, emaciation 7 %.

All of the our patients undergoing surgery of CRA had pituitary hormone deficiencies in vary combination. None of them had isolated pituitary hormone deficiency. Eleven of 16 patients had deficits of 4 or more neuroendocrine dysfunctions. Growth hormone deficiency (81.25 %), hypothalamo-pituitary-adrenal axis impairment (75 %), hypophysial hypothyroidism (68.75 %) and complete or partial central diabetes insipidus (56.25 %) were more common endocrine abnormalities in our patients.

Growth retardation may be as the initial manifestation of cranial tumors (10,11). Removal of CRA resulted in GH-deficiency in high percentage (13/16) of our patients. Some of them (6 out of 13), however, grew normally despite proven lack of growth hormone (NORMALLY GROWING GH-DEFICIENT CHILDREN). Schonsu et al reported a girl having inoperable CRA with GH-deficiency and tall stature (12,13). Undetectable growth factor or factors may be produced by the tumor (12). Thomsett et al identified

clinical evidence of growth retardation in 53 % of a childhood series and established GH-deficiency in 72 percent (14). Postoperative obesity developed in one half of our patients. Postsurgery obesity can be part of a clinical syndrome which includes hyperphagia and normal growth despite GH-deficiency (9). It is suggested that glucose-insulin-IGF-I axis may have play in this condition (15). Jorgensen et al found that IGFBP-I was quite low suggested that free IGF-I concentrations were probably at least normal. This may be explain why obese patients grow well and are not metabolically GH deficient despite low GH levels. In our CRA patients obesity index (WLI) was 114.25±25.73 in growth retarded patients, however, WLI was 131.62±34.17 non growth retarded group.

The replacement of hGH for the patient with CRA and GH deficiency is controversial (16-18). There has been increase concern regarding a possible link between GH-therapy and tumor recurrence, especially tumors of the central nervous system. In addition to increase the subsequent risk of developing leukemia and lymphoma in growth hormone treated patients (17). Fradkin et al evaluated a total of 6284 recipients of hGH distributed by the national hormone and pituitary program from 1963 to 1985, for leukemia and lymphoma developing (17). They found 6 patients of leukemia. Five of the six subjects who developed leukemia had antecedent cranial tumors (4 CRA, 1 astrocytoma) as cause of GH-deficiency. They didn't fo-

und any increase in leukemia in patients with idiopathic GH-deficiency. They noted that the association of leukemia and CRA was significant. We don't use hGH in patient with CRA and GH-deficiency.

Sklar et al noted that 25 percentage of their patients with CRA had pituitary-adrenal impairment prior to surgery (4). So that he suggested that HPA axis must be evaluated prior to surgery for prevention of acute adrenal crises, like other investigators (4,19). Steroid treatment should be commenced preoperatively, its role being two fold: firstly the correction of any hypophysial-adrenal impairment produced by tumor and secondly as a means of reducing local oedema in the vicinity of the tumor. It appear that incidence of HPA axis impairment increased after surgery like other pituitary dysfunctions. We observed HPA-axis impairment with low morning cortisol without increased ACTH values in 75 percent of CRA patients in postoperative period.

Hypothyroidism of variable degree is usual disturbance in CRA (2-5). Overt or subtle secondary hypothyroidism with low thyroxine and normal or low TSH values was found in 11 out of 16 patients. They required thyroid replacement therapy.

Undersecretion or oversecretion of vasopressine, eg, diabetes insipidus or syndrome of inappropriate secretion of antidiuretic hormone (SIADH) result in an imbalance of the salt-to-water ratio. In children this hormonal imbalance may occur secondary to suprasellar brain tumor and/or the treatment of such (2-9,20). Complete or partial central diabetes insipidus

developed in 9 out of 16 patients in the postoperative period, which was permanent in all but one child during following period (2.7 ± 2 years). None of the patient showed clinical and biochemical findings of SIADH.

Permanent or transient destruction of thirst center may be associated with diabetes insipidus in CRA. Since the osmoreceptors for thirst and vasopressin occupy contiguous areas of the anterior hypothalamus, hypodipsic hypernatremia is usually associated with defect in antidiuretic function (20). Adipsia seriously complicates the management of problems of water balance. Great care must be taken in patients with CRA complicated with diabetes insipidus and hypodipsia or adipsia. Hypernatremia due to transient loss of thirst associated diabetes insipidus occurred in only one of the our patients.

The endocrinologist usually sees the patients with CRA after surgery like us. However this is less than ideal. An evaluation of hypothalamic-pituitary axis is imperative both before and after surgery. In an ideal situation the endocrinologist should see the patients before the operation and throughout the operative and postoperative period. We conclude growth hormone, TSH and HPA axis deficiency was the most frequent finding in postoperative period. Postsurgery neuroendocrine dysfunctions were nearly doubled as previously reported incidence of these disturbances of preoperative period (4,7). Prolonged follow up with repeated endocrinologic evaluation required in all the patients.

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EDUCATIONAL NEEDS OF THE RELATIVES OF PSYCHOTIC AND DEPRESSIVE IN PATIENTS FROM TURKEY*

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SUMMARY

Psycho-educational programs for the relatives of psychiatric patients are not frequent in our country. Knowing the importance of relatives support for the patients, we decided to conduct a structured education program for the relatives. We believe that the more information they receive, the more support they give to their patients. As a matter of fact, we wanted to investigate the specific educational needs of the relatives, hence we could tailor our program to their needs. We conducted the study among the relatives of depression and psychosis patients, 20 from each group, and used a questionnaire which includes 50 questions about the way they want to receive the education. Relatives of psychotic patients reported strong interest in learning more about how to cope with "burn out" phenomenon and the negative symptoms of the illness, while the relatives of depression patients reported issues about the illness and its treatment. Both groups preferred lectures more than booklets, courses and group sessions. We found a great "educational hunger" among the relatives of patients, and then we learned about the issues that we have to touch in the educational program which we started afterwards.

Key Words: Relatives of psychotic and depressive in patients, Educational needs

Families' role and place in psychiatric disorders have moved from the "cause of the illness" to the "cause of relapses" between 1940s and 1980s. However, with the 90s, a consistent body of research has emerged suggesting that, generally, families cause neither relapse, nor the illness itself (1,2). Instead, they give us the warning signs of decompensation in their member (3). Moreover, they are sometimes so burned out by the illness of their patient that signs of decompensation could be detected in them.

In Turkey, relatives usually continue their support to their members with mental illness whatever the severity of the patient is, and as a consequence live the burden of chronic mental illness to the end. Almost every psychiatrist and psychologist, who is working with chronic psychosis (CP) patients, tries to help the families, in a structured way or not. One of the major approaches to help the families is the provision of basic information about the patient's psychiatric disorder (4). Di-

agnosis, signs and symptoms, treatment approaches, side-effects of medication and course of illness are the main information given to the families, among others. Occupational therapists have been using psychoeducation (PE) for skills training, for decades (5).

PE programs for families of the mentally ill became widespread during the 1980s as a means of providing a forum for the relevant education and mutual support of participants (6). A body of research has been conducted between late 1970s and 90s on the effectiveness of PE on delaying the recurrence of a psychiatric disorder episode (7). For example; Keegan (8) and Hovenstein (9) reported the effectiveness of PE in affective disorders. Wallace (10) and Foote et al. (11) showed the importance of PE in the management of substance abusers. Miller et al. used PE in borderline personality disorders (12). The results showed consistency from the USA to Japan and from Italy to China (13, 14).

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Naturally, schizophrenia has been one of the major areas of research on the effectiveness of PE. McGill et al. Miller and McFarlane showed the benefits of PE in schizophrenia (15, 16,17) Hogarts et al even reported a 50% reduction in relapse rates with only PE, in schizophrenics living in high expressed emotion households, and its effects persisted for 24 months, while the effects of social skills training were lost (18). PE, also, helps relatives to understand the medications (19), to attribute the causes of illness to relevant issues, which is frequently found distorted in the relatives (20), both of which may enhance patients' compliance (21). It may also reduce to stress of the relatives (22).

Second generation studies, as Goldstein noted, tested more specific hypothesis concerning the most efficient format for delivery of such programs, such as; relatives-only, single family unit, multiple family groups, etc., and found no clear-cut differences among them (7). As Birchwood et al. concluded, delivery of the information, rather than the mode of delivery, is the crucial element in the intervention (23). Nevertheless, relatives receiving education in a group acquired more information than the one received by videos and homework (23). Moreover, McFarlane and colleagues found that psychoeducational multiple family groups are not any more effective in extending remission, but also more cost-effective with a cost-benefit ratio of 1: 34 (24).

Despite the widespread clinical practice of educating the patients and relatives about psychiatric illness, relatively little is known about the specific educational needs of these patients and relatives (4). The curriculum of most educational programs, including ours, has been established by treatment providers, based on their beliefs as to what information about the illness and its treatment patients and families needs to know, rather than on objective data collected from the patients and relatives themselves. It appears to be a major flaw of the educational programs.

In the Psychiatry Clinic of University of Ankara, Medical School (UAMS), we have conducted PE programs for years, but it has mostly been for the patients. Although the importance of PE for the relatives has long been known, a structural PE has not been established until now. Families are welcomed to group psychotherapy sessions, where they can receive some information on the illness of their members, but also share feelings, experiences and naturally receive support. These groups, although highly effective, can not

be taken as PE groups. As a matter of fact, we decided to establish a structured and continuous PE program, and as mentioned above, wanted to base it on the objective needs of the consumers.

Thus, the aim of this study is to evaluate the specific educational needs of the relatives of schizophrenia and depression patients, the two most prevalent diagnosis in our inpatient wards, and probably the ones who most needed PE. We also wanted to learn the modes of PE presentation that they prefer most, since the way we see for years (lectures) might not be the most suitable one.

METHOD

The study is conducted in the Psychiatry Clinic of UAMS, in the first half of 1995. The subjects for this study comprised 60 relatives of inpatient chronic schizophrenics and major depression patients, 30 from each, admitted to our clinic's inpatient wards for male and female psychotics. Half of all patient groups was male and half was female. To be included in the survey, relatives were required to live with the patient and to have an education of at least 5 years. One relative for each patient was included and was explained the nature of the study before completion of the questionnaire. Most of the relatives were parents (65.0%), followed by spouses (18.4%), siblings (13.3%) and children (3.3%). Groups were almost similar on this matter.

Since the number of major depression patients admitted to our wards for psychotics is relatively low, it took about half a year to complete the study. We tried to include every one relative of all admitted patients for not to be biased. No relative declined to complete the survey, but about 10% had to be replaced by new subjects, because of incomplete fulfilling of the questionnaires.

A questionnaire was developed by the authors to assess the educational needs. Fifty items pertaining to different areas of educational need were generated by a group of five professionals, and questions from previous surveys (4) were used but with the addition of new items relevant to Turkish culture. They rated their interest in learning more about each item on a five point Likert-type scale, with 1 denoting "not interested" and 5 denoting "very interested". Relatives were also encouraged to write additional topics they wanted to be educated, not covered by the 50 items. Finally, relatives were asked to present their preferences

Table 1: Various Characteristics of the Relatives and Patients

	Major Depression Group (n=30)	Schizophreni A Group (n=30)
Age of the Patient	33.5±9.6	30.5±10.1
Age of the relative	46.1±11.6	48.3±12.5
Education of the Patient	11.0±3.7	9.9±3.1
Education of the Relative	9.7±2.7	9.8±2.9
Duration of Illness	1.7±0.8	6,1±3.7
Number of Hospitalization	1.2±0.4	2.0±1.1

on the mode of receiving this education. They rank ordered 4 items; Lectures (one hour a week), booklets, group sessions (include discussions and sharing of experience, one or twice a week), courses (a week long course twice or three times a year). Again, they were encouraged to note down any other mode that is not mentioned.

Since the motive of the study was to investigate the nature of the educational needs of the relatives of both schizophrenia and major depression patients, no statistical analysis is performed in order to compare the groups.

Another part of this study is the evaluation of patients' educational needs with the same questionnaire, which is presented in another paper (25).

RESULTS AND DISCUSSION

Tables 1 and 2 outlines the socio-demographical features of the relatives and the patients. Patients are in

their early thirties, while their relatives are in late forties. For the educational levels of the subjects, there is a very slight difference between the relatives but schizophrenics appeared to be less educated than the depressive patients.

A high percent of patients is found to be married (60%), but it is even higher in their relatives (81%). This finding is more obvious in the depression groups. When we evaluate the occupational status of the subjects, we can find a high rate of unemployment, which more prevalent in relatives than patients, and in schizophrenic patients than depressives. The cause of the unemployment in the relatives may be retirement, which can be achieved very early in Turkey, or being a housewife, which is also very prevalent among women in Turkey. For the schizophrenics, it may be a direct consequence of a schizophrenia, which can lower functioning in some patients severely.

Table:1 also outlines the duration of the illness and the number of hospitalizations for both groups. Schizophrenics are found to be obviously more chronic than the depression patients, but the differences between the mean number of hospitalizations is not that apparent, which may imply similar severity despite different chronicity.

In Table: 3, the rank order of educational topics made by major depressions patients is outlined. "Early warning signs of relapse" is the most rated item in the list which indicates a healthy concern on the relapse prevention by the relatives. "Psychiatric medication" and their "Side effects" followed the signs of relapse. The relatives appeared to be concerned on the "drugs" which their child or spouse regularly takes.

Table 2: Marital Status and Occupations of the Relatives and Patients

	Major Depression Group (n=30)		Schizophreni A Group (n=30)	
	n	%	n	%
Married Patients	21	70.0	15	50.0
Single Patients	7	23.3	12	40.0
Divorced/Widow Patients	2	6.7	3	10.0
Married Relatives	25	83.4	24	80.0
Single Relatives	1	3.3	2	6.7
Divorced Relatives	4	13.3	4	13.3
Unemployed Patients	11	36.7	14	46.7
Employed Patients	19	63.3	16	53.3
Unemployed Relatives	15	50.0	17	56.7
Employed Relatives	15	50.0	13	43.3

The first three ratings have some similarity with the Mueser et al.'s 1992 survey, except that they found "Side-effects of medications" as the number one rated item and "psychiatric medications" as the second. They also ranked items, such as "how psychiatric diagnoses are made" and "getting what you need from the mental health system" at numbers four and five, which our relatives did not rank higher.

The fourth item on our rank order is the "Genetics...", which may imply a subtle concern of responsibility of the relatives. This finding is very interesting, since we did not expect it to be this high. We have to include genetics and its role in the etiology of depression to our PE program. Other items high on our list are the ones concerning coping skills with the symptoms of illness, like, anhedonia, anxiety, suicide, sadness, etc.

In Table: 4, the rank order of educational topics made by relatives of schizophrenics is outlined. "Coping with social isolation and withdrawal" became the number one rated item, followed by three other negative schizophrenia features at #2, #7 and #9. These findings imply the burden of relatives living with a schizophrenic, who had a mean of 6 years of illness. Similarly, "Managing burn-out" became the third item on the list. However, "Social isolation" and "burn-out" did not appear in the top twenty of Mueser et al.'s list (4), which may be a result of differences between patient groups, relatives or cultures. They found "Side effects of medication" as the most rated item, followed by "Getting what you need from the mental health system" and "Setting limits on the patient's behavior", which are absent in the top twenty of our list.

We would not be surprised to find items like "psychiatric medication" and "side effects" at the top of the list, since they are the questions relatives mostly ask to us. However, "side effects" became #10 and "psychiatric medication" #13, while ECT became #5, which is a surprising but important finding. We must not give more time to medication than it is required, and not forget the ECT.

There are also several differences between the two diagnosis groups' ratings. Relatives of depression patients were more interested in treatment approaches, while relatives of schizophrenics reported a need to learn more about coping strategies on various issues, particularly negative symptoms of schizophrenia. These results may be reflecting the nature of patients' condition. Schizophrenia patients are all chronic cases

Table 3: Educational Topic Ratings of Relatives of Major Depression Patients

Rank	Item	Mean
1	Early warning signs of relaps	4.73
2	Side-effects of the psychiatric medication	4.50
3	Psychiatric medications	4.43
4	Genetics and vulnerability to psychiatric disorders	4.36
5	Coping with sadness, hopelessness and pessimism	4.36
6	What the illness is like for the person with it	4.33
7	Coping with loss of pleasure	4.26
8	Coping with suicidal thoughts	4.23
9	The impact of stress and life events on the illness	4.23
10	Coping with anxiety	4.03

Table 4: Educational Topic Ratings of Relatives of Chronic Schizophrenia Patients

Rank	Item	Mean
1	Coping with social isolation and withdrawal	4.53
2	Improving social relationships	4.47
3	Managing burn-out	4.43
4	Strategies for solving problems	4.33
5	Electroconvulsive therapy (ECT)	4.33
6	Coping with stigma of psychiatric illness	4.30
7	Coping with anhedonia	4.23
8	Early warning signs of relapse	4.20
9	Coping with lack of interest and motivation	4.20
10	Side-effect of the psychiatric medication	4.16

with a mean of 6 years of illness, so their relatives might have already educated on the treatment, either actively or not. They are now hungry for the information on the management of residual symptoms or burn-out and stigmatization. However, relatives of depression patients are more anxious on the treatment issues. On the other hand, in the second part of this survey, Sayil et al. found contrasting results with the patients; schizophrenics rated medications and their side-effects, while depressives rated coping skills higher.

Last table outlines the preferred modes of education presentation by the relatives. Both groups rated "lectures" on top, but relatives of depression patients rated "booklets" and schizophrenics "group sessions" as the second mode. Lectures are the usual mode of education presentation of our PE programs, but reports

Table 5: Relatives Preferences on the Mode of Education Presentation*

	Major Depression Group (n=30)	Schizophrenia A Group (n=30)
Lecture	2.0±1.2	1.9±1.0
Group Sessions	2.6±1.3	1.9±0.5
Booklets	2.4±1.0	2.7±1.3
Courses	3.0±0.8	3.5±0.7

* Since it is a rank order, from 1 to 4, low mean indicates high preference

from other authorities indicate the usefulness of family groups (17). However, our subjects did not prefer groups as much as lectures. It may be the result of unfamiliarity of persons with group sessions in Turkey. Lectures, however, have the potential of passifying the listeners, which may end up decreasing their own problem solving capabilities. A PE program should not overlook this potential danger, and whatever the mode of education is, it should foster their sources.

Group sessions are still present in our arsenal and they should be kept going, not only for they have been sorted high in our survey, but for the compensation of "emotional" part of the experiences of the relatives. They may find soothing answers for their questions in a PE hour, but may not find the universality, altruism, instillation of hope and most importantly, ventilation and catharsis, that a group session can provide.

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Courses are favored by neither of the groups, which can be understandable since they are difficult to attend for people who a regular job, and since they are not as frequent as lectures or groups. Booklets, however, ranked high in our study, especially in the depression group. They are practical sources of information for they can be carried to anywhere with the holder. Our department had released a booklet for schizophrenics previously, which was welcomed by both the patients and relatives. However, booklets can not answer all questions and carry the potential of misunderstanding, which can be solved easily in a face to face modality.

CONCLUSION

This survey of relatives' educational needs emphasizes the importance of assessing the specific needs of the different diagnostic groups. Patients and relatives are capable of identifying their educational needs, and these perceptions need to be accommodated in order for providers to overcome the dissatisfaction of mental health consumers with current treatments. If we are to promote the dialogue between patients, families and mental health professionals, we would be advised to design educational programs based on objective data collected from the mental health consumers (4). Finally, as Keegan and Walsh noted, these PE programs have to be evaluated regularly for their effectiveness, and we should build knowledge from each preceding class and try to be interesting, relevant and fun.

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THE CAUSES AND TREATMENT OF PSYCHIATRIC DISORDERS AS SEEN BY PATIENTS*

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SUMMARY

Etiologic concepts of psychiatric patients are known to have great impact on the course and outcome of their illness but they have been investigated less frequently than their relatives (1). The aim of this study was to determine the perspectives of patients on causes and treatment of their illness. There are four groups which are consisted of 30 patients suffering from schizophrenia, depression and psychonevrosis patients, plus 30 'normal' volunteers. We applied two questionnaires, one for the attributions on the causes of illness, and one for the treatment. Results showed that, a high percentage of patients in all groups had visited extra-medical persons and places. Besides, we found out that they still believe in esoteric causes, but they search treatment in psychiatry. We concluded that patients (especially psychotics) need to be informed on the causes and the available treatment approaches because they not infrequently attribute to irrelevant issues.

Key Words: Causes of psychiatric disorders, Exta-psychiatric treatments

Patients who attribute their illnesses to irrelevant causes may search for extra-psychiatric or psychological treatments and show non-compliance with the treatments. Moreover, patients who have ascetic beliefs or blame for themselves may not search any treatment at all and if obliged, give it up as soon as possible. Attributing the cause of illness to irrelevant issues and searching treatment from extra-medical sources, para-professionals, religious or quasi-religious persons are supposed to be highly prevalent in Turkey. While there is no reliable statistics on this subject, our experience suggests about a 50% visited an extra medical person among psychiatric patients. These visited persons are usually some old people who had a reputation of "healing". They are very frequent and omnipresent in Turkey and they can sometimes really heal various psychiatric problems, mainly hysterical originated ones. It is unfortunatane because it feeds their reputation. On the other hand religion is a major phenomenon especially in the rural parts of Turkey and we

know that individuals' religious beliefs sometimes can interfere with their health behaviours (2).

MATERIAL AND METHOD

This study was conducted in the Psychiatry Clinic of University of Ankara, Turkey, in the first half of 1995. We randomly selected 30 schizophrenics and 30 depressives from our inpatient wards, 30 psychoneurotic patients (anxiety and somatoform disorders) from our outpatient department and finally 30 "nominal" persons as a control group for gender, age and education levels, the main variables that were likely to influence the results other than illnesses.

Two questionnaires and one demographical data form were used in the study, all prepared by the researchers in the light of relevant literature and Turkish Culture. These two questionnaires consisted checklists about the causes and treatments of psychiatric disorders. The frst one had 57 items on the etiologic issue.

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Patients pointed their opinions on whether that item could be a cause of a psychiatric disorder or not on a 3-Point-Likert type answer sheet, like "I Agree", "Neutral" or "I Disagree". The 57 items were divided into 5 major topics; "Biological causes", "Familial causes", "Psychosocial causes", "Personality causes" and "Esoteric causes". The other questionnaire was a rather short one (15 items), scanning for the beliefs of subjects on the treatment of psychiatric disorders. It was answered as mentioned above but consisted 4 subgroups; "Medical treatments", "Esoteric treatments", "Psychological growth" and "Environmental changes".

"Biological causes" subgroup included 14 items like; head trauma, infections, malnutrition, organic brain dysfunction, hereditary, etc. "Familial causes" included 13 items like; broken family overinvolved mother/father, over criticism from the family, etc. "Psychosocial causes" mainly referred to recent life events, like; losing a job, changes in residency or school, financial problems, etc. and included 17 items. "Personality causes" included 9 items, like; lack of willpower, being too ambitious, being too inefficient, failure in life, etc. Finally, "Esoteric causes" included 9 items, like; possession of evil spirits, result of sins or crimes, horoscope, supematural powers, black magic, bad faith, etc. Since several items fall into multiple subgroups, the total number (62) exceeds 72.

For the attributions of treatment; "Medical treatments" (4 items) included; drugs, psychotherapy, electro convulsive therapy and hospitalization. "Esoteric treatments" included 3 items; improving religious practices, visiting "healers" and a ritual for sending away bad luck or bad faith implanted by evil people. "Psychological growth" (4 items) referred to improving willpower and personal strength. "External solutions" (5 items) included changes in the very environment, financial status or (fantastically) past.

In the demographical data form, patients were also questioned for their religious beliefs and extra-medical treatment searches. Scores of the two questionnaires were as follows; 1 for Agree, 2 for Neutral and 3 for Disagree. Thus, higher points indicate disbelief on the written causes or treatments. We calculated the total points they scored for the subgroups and compared the patient and control groups with students' t-test. Division of total point of one subgroup to the number of items gave the weighted scores which show the inclination of patients clearly.

RESULTS AND DISCUSSION

Table 1 shows the demographical features of the subjects. Statistical analysis was made for only age, educational years and gender (chi-square for gender, t-test for others) and we found no significance.

In Table 2 subjects' religious and extra-medical searches are outlined. According to this table, most of the subjects in all groups practice religion moderately but many of them had visited some sort of extra-medical source for help, even the "normal" group. This finding proves the high affiliation of Turkish people with non-medical, spiritual issues. These findings would be higher, if the study was conducted in a rural settlement. Another striking finding was the high percentage of patients referring to relevant publications available to them. Television programs could also be ranked highly. This result is important for the psychoeducation programs; they can publish materials for the patients with an ongoing process and get satisfactory results.

Table 3 outlines the questionnaire on causes, with statistical analysis between each group of subjects. We can see from this table that; schizophrenics were mostly undecided on the causes of illness, nevertheless placing biologic and esoteric causes slightly back and

Table 1: Demographical Features

n= 30 for all	Schizophrenia	Depression	Psycho Neuroses	Controls
Gender (Male)	50.0%	43.3%	46.7%	50%
Marital Status (Married)	33.3%	33.3%	56.7%	46.7%
Occupation (Employed)	60%	43.3%	46.7%	100%
AGE*	29.8	32.3	30.5	29.3
Education*	9.5	9.8	8.1	10.2
Duration of Illness*	6.5	4.6	5.1	-
Number of Hospitalizations	2.9	2.2	0.3	-

* Mean years

Table 2: Religious and Extra-Medical Treatment Searches (%)

n= 30 for all	Schizophrenia	Depression	Psycho Neuroses	Controls
Religious Practices				
Frequent	36.7	33.3	46.7	20.0
Moderate	60.0	66.7	53.3	73.3
Ve Few / None	3.3	0.0	0.0	6.7
Extra-Medical Help				
Healer, sacred place	53.3	66.7	46.7	26.7
Fortuneteller	16.7	10.0	40.0	26.7
Meditation	0.0	3.3	0.0	3.3
Psychology books*	56.7	53.3	73.3	23.4
None	16.7	13.3	20.0	33.3

* Plus; newspaper articles, scientific articles, psychiatry books; etc.

psycho-social issues a little forward. They and depressives put significantly less emphasis on biological, family, psychosocial and personality causes than controls but more emphasis on esoteric causes. This result is in accordance with a similar study conducted in our clinic 13 years ago (3). Schizophrenics and depressives did not differ significantly on any subject between each other. Depressive patients mainly reported psycho-social issues as the cause of illness (object losses) as expected but disregarded negative family conditions and biological causes. Neurotic patients, on the other hand, put blame on their own personalities and did not generally agree with other causes. Given the high frequency of their religious practices and "healer-fortuneteller" experiences, this finding is somewhat contradictory. Maybe, getting rid of being exploited by the healer-type of persons, they began to attribute their problems to their own personalities, rather than fate.

They also did not score biological causes, which may be a result of increased awareness of the psychogenic origins of their problems, within the years. Finally, even though controls reported extra-medical experiences not so infrequently, they did not give credit to the esoteric causes, instead they pointed the other causes almost homogeneously. This may be a result of inexperience and/or undereducation on such disorders.

Table 4 shows the opinions of patients on treatment issues. It is of great interest that neurotic patients chose medical treatments significantly less than other groups. They mostly place external changes significantly higher which is a bad sign of prognosis. All three patient groups rank personal changes higher (but nevertheless not as high as controls) and did not show difference. Schizophrenics' and depressives scoring higher on esoteric treatments than controls and neurotics is another issue of importance. This means, while

Table 3: Attributions: on Causes of Psychiatric Disorders

	Schizophrenia	Depression	Psycho Neuroses	Controls	Statistics
Biological	22	2.4	2.5	1.4	*S/C, D/C, P/C **S/P
Family	2.1	2.3	2.6	1.3	*S/C, D/C, P/C *S/P ***D/P
Psychosocial	1.9	1.8	2.5	1.4	*S/C, P/C *S/P, D/P **D/C
Personality	2.0	2.1	1.9	1.5	*S/C, D/C, P/C **D/P
Esoteric	2.2	2.1	2.5	2.4	*D/P **S/P, D/C ***S/C

* : p<.001

** : p<.01

***: p<.05

S: Schizophrenia

D: Depression

P: Psychoneuroses

C: Controls

Table 4: Opinions on the treatment of psychiatric Disorders

	Schizophrenia	Depression	Psycho Neuroses	Controls	Statistics
Medical	1.9	1.6	2.1	1.3	*S/C, P/C, D/P *D/C ***S/D, S/P
Personal	1.5	1.7	1.6	1.1	*S/C, D/C, P/C
External	2.0	1.9	1.4	1.9	*S/P, P/C **D/P
Esoteric	2.2	2.2	2.7	2.8	*S/C, D/C, D/P **S/P

* : p<.001 ** : p<.01 *** : p<.05
S: Schizophrenia D: Depression P: Psychoneuroses C: Controls

they believe in the benefits of medical treatments, they do not give up alternative ones. The fact that we included religion in this group might be increasing the result. Nevertheless it should not be overlooked.

CONCLUSION

Patients' and sometimes their relatives' attributions to the causes of illness and their opinions on the treatment methods are usually overlooked by the clinicians. We suppose that; "they know many things and can always think rationally" and the worst of all; "they will accept and obey our suggestions and explanations readily". These myths can break the patient-clinician relationship and result in non-compliance, drop-outs and even symptom exacerbation. We have to give enough time to the thoughts of the patients. This study was made in order to give systemic support to the presence of great diversity and unpredictability in patients' attributions and opinions on causes and treatment of their illnesses.

In fact, we found that biological causes and even treatments (which became the widely accepted explanation and treatment approach in contemporary psychiatry) are poorly accepted by the patients. Most of them are still uncertain about the organic aspects of their illnesses. Whether it is *really* organic in or not, patients learning this information usually get comfort from it. Because he/she is not responsible from the disorder. They feel less guilty and depressed and become more oriented to their treatment regiments. Esoteric causes have somewhat similar consoling effect (li-

ke blaming it on fate) but they can interfere and as our experience proved occasionally, sabotage medical treatments. Attributing causes and treatments to external events may just as well have the similar negative effects on patients. The more patients are inner oriented and had inner locus of controls the more they would benefit from the treatments (4).

The high range of religious and alternative medicine experiences we observed are somewhat in accordance with the literature, especially American literature (2,5). Some writers suggest clinicians to pay attention to their patients' spiritual sides (6,7) even if it seems just the opposite of us but this does not mean that we should let them uninformed about the modern treatment approaches. Contemporary Western Psychiatry has already integrated psychoeducation programs into their practice and began to get their fruit (8,9,10,11). Since patients and their relatives actively search for explanations for the occurrence of psychiatric disorders, clinicians are well advised to take the initiative and to discuss this issues. It would certainly affect their help-seeking behavior (12). In our clinic we do have various but not standardized patient education programs. With the help of studies like this one, we try to shape and revise it.

This study could have been better with more patients included and using reliable and valid inventories, instead of questionnaires, but nevertheless it gives us an insight of the importance of patients' concepts on such issues. We plan to expand it with the inclusion of families, questions on educational needs in order to clarify this vital issue.

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THE EFFECT OF PROSTATITIS ON PROSTATE-SPECIFIC ANTIGEN

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SUMMARY

The objective of this study is to investigate the possible effects of prostatitis on prostate - specific antigen (PSA) concentration. PSA levels were measured in 54 selected patients with prostatic infection and no incidence of benign prostatic hyperplasia (BPH) and prostatic cancer. PSA levels were found to increase (over 4 ng/ml) in 4 of 5 (80%) patients with acute prostatitis, in 4 of 19 (21%) patients with chronic bacterial prostatitis and in 3 of 20 (15%) patients with abacterial prostatitis. PSA levels returned to normal by antibiotherapy in 8 patients with acute and chronic bacterial prostatitis and 3 patients with chlamydia infection.

Conclusion: When PSA is referred to as a tumor marker, it should be noted that coexisting prostate inflammation may contribute to a rise in PSA levels without any malignancy.

Key Words: Prostatitis, Prostate infection, Prostate - specific antigen, PSA

Researchers who identified the existence and characteristics of prostate - specific antigen (PSA) in 1980, after a forty year pursuit of an ideal tumor marker, have also stated that it is a valuable marker for prostatic adenocarcinoma (1,2).

PSA, which is a serine protease, is produced by benign and malignant epithelia cells of the prostatic gland. This means that the marker is organ-specific but not cancer specific (3,4).

PSA has a considerably high concentration in the seminal fluid and it facilitates the liquefaction of seminal coagulum after ejaculation. It is a valuable marker for detection, staging and follow-up of prostate carcinoma. The biologic half-life is 2.2 - 3.2 days and the normal range of PSA in adults is between 0-4 ng/ml (5-6). It has been reported that digital rectal examination, prostatic massage, transrectal ultrasonography and ejaculation don't cause any statistically significant changes in serum concentration (7,8).

Prostatitis is inflammation of the prostate gland. Drach et al. defined prostatitis with the existence of more than 10 leukocytes for each high-power field in the microscopic examination of prostatic secretion

and classified 4 types of prostatitis according to symptoms, digital rectal examination findings, microscopic examination of prostatic secretion and bacterial culture documentation; acute bacterial prostatitis, chronic bacterial prostatitis, chronic non-bacterial prostatitis and prostatodynia (9). Although prostatitis is detected in nearly 5 out of 1000 men per year, the incidence may rise up to 75% in prostate specimens (10). Neal et al. have reported significant increases in serum PSA levels of test animals, 5 -7 day after the instillation of infected saline into the urethra of these animals (11).

The purpose of our study is to examine the serum PSA levels in a selected group of patients with prostatitis who have not demonstrated the occurrence of benign prostatic hyperplasia and prostatic carcinoma and to investigate the effects of prostatitis on serum PSA concentrations

MATERIALS AND METHODS

Between January 1995 and October 1996, 54 patients ranged between 21-52 years old (mean 37) and together with symptoms of prostatitis were included in

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the study. They were suffering from acute or recurrent pelvic, scrotal and perineal pain. Dysuria, pollakiuria, nocturia, and urgency were not evident except the patients with acute bacterial prostatitis. Digital rectal examination (DRE), transrectal ultrasonography (TRUS), microscopic examination and bacterial culture documentation of prostatic secretion were performed according to Stamey and Meares (12). In view of this results, prostatitis was determined according to Drach et al. (9). Serum PSA concentrations were measured with monoclonal radiometric immunoassay at the time of diagnosis, before physical examination and 6-8 weeks after antibiotic treatment of the patients with bacterial prostatitis. Enzyme immunoassay (EIA) test revealed *Chlamydia trachomatis* in the prostatic secretion of 14 of 20 (70%) patients with non-bacterial prostatitis. These patients were treated with doxycycline or ofloxacin for 4 weeks. Two of six patients, who were suspected of having prostate carcinoma, underwent transrectal needle biopsy and tru-cut biopsy was performed for the other four.

RESULTS

The type of prostatitis and bacteria responsible for infection was shown in (Table 1). Increased PSA levels (over 4 ng/ml) were found in 4 of 5 patients (80%) with acute bacterial prostatitis and 4 of 19 patients (21%) with chronic bacterial prostatitis and 3 of 20 patients (15%) with non-bacterial prostatitis. PSA levels were below 4 ng/ml in all the patients with prostatodynia (Table 2). Histopathological examination of 6 patients who had undergone prostate biopsy because of suspicious digital rectal examination or TRUS has revealed

the existence of chronic inflammatory changes and no carcinoma. Prostate secretion cultures became sterile in 22 of 24 patients with acute or chronic bacterial prostatitis and 12 of 14 patients with chlamydia after the treatment of these patients with effective antibiotics for four weeks (Table 3). Serum levels of PSA returned to normal values (below 4 ng/ml) 6-8 weeks after the end of antibiotic treatment.

DISCUSSION

Beside prostate carcinoma, serum PSA levels may also exhibit an increase due to various manipulations like cystoscopy, prostate biopsy and as a result of non-malignant diseases such as acute urinary retention, benign prostate hyperplasia (BPH) and prostatitis (12-14). PSA may rise in case of any disruption in the prostatic basal cells, the epithelial basal membrane, the prostatic stroma, the capillary basal membrane and the capillary endothelial membrane (15). Palou et al. have reported a 24% incidence of acute bacterial prostatitis and 3.3% incidence of chronic bacterial prostatitis in patients with elevated PSA values (13). However, they did not evaluate the existence of benign or malignant diseases and they were not in specific age limit. So it was difficult to achieve a clear differentiation. Prostatitis can probably increase vascular permeability and lead to cellular death which may in turn facilitate the diffusion of PSA into the bloodstream (15). In a study in which histopathological examination of non-selective autopsy specimens was carried out, prostatitis was found in 6.3% of the cases (13). Kohen et al. have identified a very high incidence of (98%) inflammatory changes after the histopathological examination of the

Table 1: The type of bacteria causing prostatitis.

	E. coli	K. pneumonia	E. faecalis	Staf. aureus
Acute bacterial prostatitis	3	1	1	-
Chronic bacterial prostatitis	11	1	2	5

Table 2: PSA levels of patients with prostatitis. (ng / ml)

	>4 ng/ml		2.5 - 4 ng/ml		>2.5 ng/ml	
	n	%	n	%	n	%
Ac.Bacterial Prostatitis (n=5)	4	80	1	20	5	100
Chr.Bacterial Prostatitis (n=19)	4	21	4	21	8	42
Chr.Abacterial Prostatitis (n=20)	3	15	6	30	11	45
Prostatodynia (n=10)	-	-	4	40	4	40

*P<0.05 Acute bacterial prostatitis with chronic bacterial prostatitis (According to Fishers exact test)

Table 3: The results of prostatic fluid culture after antibiotherapy.

	Culture (+)	Culture (-)
Ac.Bacterial Prostatitis (n=5)	-	5
Chr.Bacterial Prostatitis (n=19)	2	17
Chr.Abacterial Prostatitis (n=14)	2	12

specimens from the patients with BPH and who had gone through prostate resection (16). Chronic prostatitis may coexist in 60% of the patients with BPH and PSA levels may exceed 10ng/ml (17,18). Brawer et al. have reported that 11 of 35 patients who underwent prostatectomy for BPH were seen to have PSA values above 4 ng/ml and they have concluded that the underlying reason was the inflammation of the gland (19).

There is a significant relationship between PSA levels and prostate inflammation in both acute and chronic prostatitis (20). In addition to this, during the digital rectal examination, confusion of prostatitis with malignant prostate diseases is more common than confusion with benign diseases (21). In their study covering 72 cases with prostatitis and 50 years of age, Pansadora et al. have reported elevated serum PSA levels (above 4 ng/ml) in five out of 7 (71%) patients with acute prostatitis, in two out of 13 (15%) patients with chronic prostatitis in two out of 32 (6%) patients with non-bacterial prostatitis (22).

In our study, there were 54 patients with no BPH and carcinoma. Increases in PSA were measured in 80%, 21% and 15% of the patients with acute prostatitis, chronic bacterial prostatitis and chronic non-bacterial prostatitis respectively. When these results and similar findings in the literature are evaluated, it can be inferred that prostatitis induces PSA increment and

this effect is more pronounced in acute prostatitis. When we take into account that the mean age of the patients in our study group was 37 (only one man 52 years old, the others below 50), we may consider the reference range of 0 - 4 ng/ml PSA too high for the patients under 50. Oesterling et al. have determined the normal age-specific upper limit of PSA for a healthy population to be 2.5 ng/ml between 40 and 49 years of age (23). In a similar study which included 100 healthy men between 20 -29 ages (mean 26), 2.6 ng/ml was measured as the normal upper limit for PSA (6).

In this study, PSA values between 2.5 and 4 ng/ml were found in one patient with acute bacterial prostatitis, 4 patients with chronic bacterial prostatitis, 6 patients with chronic non-bacterial prostatitis and 4 patients with prostatodynia. When we re-evaluate our results with respect to age-specific normal values, we find increased PSA in 5 of 5 (100%) patients with acute bacterial prostatitis, in 8 of 19 (42%) patients with chronic bacterial prostatitis, in 9 of 20 (45%) with chronic non-bacterial prostatitis and in 4 of 10 (40%) patients with prostatodynia (Table 2). The fact that serum PSA was increased in significant number of cases (in a selected group of patients with no BPH or carcinoma) and it returned to normal values after an effective antibiotherapy. These findings supported the literature findings that the underlying reason is the inflammation of the gland.

As a conclusion; prostatitis can cause high PSA levels and this effect more prominent in patients with acute bacterial prostatitis. Prostate inflammation may accompany prostate carcinoma in most of the patients. For these reasons, when using PSA as a tumor marker, we believe that it will eliminate possible misdiagnosis if the existence of prostate inflammation is evaluated.

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PLACE OF HEMIARTHROPLASTY IN TREATMENT OF INTERTROCHANTERIC FRACTURES OF ELDERLY PATIENTS

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SUMMARY

In the two years between 1992 and 1994, hemiarthroplasty has been performed to 48 patients with intertrochanteric fractures whose mean age was 79. To 6 of these Thompson unipolar type hemiarthroplasty was applied while to the remaining 42, various types of bipolar hemiarthroplasties were preferred. Mean follow-up period was 22 months. 4 of the patients died in the early perioperative time. We have observed that the mortality rate was high at the end of the first year due to the high mean age, low physical activity and general health status, and various other medical problems. But the possibility of early mobilization and decrease in the other complications caused by internal fixation, showed the superiority of hemiarthroplasty application in cases of elderly patients with comminuted intertrochanteric fractures.

Key Words: Hemiarthroplasty, Trochanteric fractures

One of the problems which mostly affect the elderly population, and which is still waiting for solution for its complications, is the intertrochanteric fractures. The impossibility of application of conservative treatment and the high incidence of complications like decubitus ulcers, emboli, urinary and cardiopulmonary disorders which may occur during treatment lead to search for new treatment modalities. The classical and successful treatment for intertrochanteric fractures is possible with stable osteosynthesis. But this depends on the degree of osteoporosis, type of the fracture, and the type of the chosen fixation device. Thinking of the "early range of motion, late weight-bearing" principle, the stable osteosynthesis increases the rate of morbidity and mortality of the elderly patient who already has cardiopulmonary problems, thus bringing up the choice of arthroplasty. Since acetabular degenerative changes are present in most of these patients, arthroplasty is undoubtedly an alternative treatment to internal fixation.

In this study we have presented the retrospective assessment of morbidity and mortality incidence in the elderly patient group, who had intertrochanteric frac-

tures, and who had hemiarthroplasty as treatment, in our clinic.

MATERIAL AND METHOD

In the two years between 1992 and 1994 48 patients with intertrochanteric fractures were treated by the application of various types of endoprotheses in the Ankara University Faculty of Medicine Ibn-i Sina Hospital Department of Orthopaedics and Traumatology. 35 of the patients were female and 13 were male, the youngest being 75 and the eldest 102 years old. Mean age was 79. 28 of the fractures involved the left hip while the other 20 were at the right hip. All of the fractures involved the trochanteric region. 42 (87.5%) of the fractures were caused by falling down, and 6 (12.5%) by traffic accidents. Pathological fractures were not included in the study. The mean follow-up time was 22 months.

Fractures were classified due to Evans classification method. According to this classification method, 36 (75%) of the cases were displaced and nonreducible, 5 (10.4%) were displaced but reducible, 4 (8.4%) were comminuted, and 3 (6.2%) were non-displaced.

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All of the patients were assessed preoperatively for medical problems. Except 7, all the patients had one or two of the common geriatric disorders like hypertension, arteriosclerotic heart disease, diabetes mellitus, congestive heart failure, and previous cerebrovascular accident. Patients were appropriately medicated before the operation to optimize the general health status and to control the associating disorder. All of the patients, if any contraindication did not exist, were given prophylactic antithrombotic treatment with low molecular weight or mini-dose heparin, starting from the first day of admission to the hospital, until the time they were fully mobilized.

Operation timing was approximately 6 days (3 to 15 days) after the admission to the hospital. 30 minutes prior to the operation prophylactic antibiotic treatment was began to be given. For this purpose 1st generation cephalosporins (mostly Cefalotin 1 g/day intravenous) were used.

Spino-epidural anesthesia was applied to 42 (87.5%), and general anesthesia to 6 (12.5%) of the patients. For 47 of the cases lateral and for one case posterior approach was preferred. Prosthesis was implanted and placed in neutral to slight anteversion and neutral position. Fixation of the prosthesis in the femoral shaft was carried out using femoral shaft plugging and insertion of bone cement under manual or pressure technique. Stability was tested perioperatively. If the hip could be rotated externally 45° at full extension and maximally rotated externally at 30° flexion without luxation, the prosthesis was justed stable. Roentgenograms evaluating the position of the prosthesis were made routinely intraoperatively and on the second postoperative day.

To 6 (12.5%) of the cases Thompson, and to the remaining 42 (87.5%) various kinds of bipolar endoprostheses, all cemented, were applied (Figure 1,2). Mean operation time was 45 minutes (30 to 90 minutes), Approximately 0.5 to 1 units of whole fresh blood was used per patient. Aspirative drain was put to all of the cases and was removed in the first 24 to 48 hours. Prophylactic antibiotic treatment was continued two days postoperatively. To both of the lower extremities of the patients elastic bandage, and to the operated extremity, position boot splint was applied immediately after the operation.

The patients were seated at the second postoperative day after the routine wound care procedure. On the third day they were allowed to walk giving full weight to the operated extremity. The mean hospitalization time was 13.5 days (5 to 21 days).

RESULTS

4 (8.3%) of our patients have died in the early postoperative period (1 to 3 days postoperatively). The reason of exitus in 2 of the cases was decompensated heart failure and in the other 2 gross pulmonary emboli. 6 (12.5%) of the patients have died in the first 12 months. The reasons were cardiovascular failure for one, thromboembolic disease for another, and cerebrovascular accident for the other patient. 6 (12.5%) of the patients died of cardiopulmonary and cerebrovascular disorders after the first 12 months. The remaining 32 patients were followed up for a meantime of 22 months.

Superficial wound infection was observed in 3 (6.25%) cases. They were cured by appropriate antibiotic treatment. Deep tissue infections did not occur.

In spite of the precautions taken in advance, decubitus ulcers developed in 8 (16.7%) patients until the time of the operation. They had cure by postoperative early mobilization and the appropriate treatment. Brooks type II to III heterotopic ossification developed in 2 (4.2%) cases.

We have observed apparent acetabular erosion in 4(13.3%) patients during the follow-up period. 2 of the cases had Thompson endoprostheses, while the other two had bipolar endoprostheses. 2 of them, later, had undergone total hip arthroplasty. We observed no luxation, loosening of the stem or late infection.

24 (80%) of the total 30 patients who had 22 months of follow-up returned to physical activity levels close to the pre-fracture times within the postoperative 6 months. In the 4 of the remaining 6 cases serious hip pain due to acetabular erosion, and in the other 2 cases hip pain and diminished range of motion due to heterotopic ossification had developed.

DISCUSSION

Selection of the operation technique for the surgical treatment of the trochanteric region fractures depend on the age and the general health status of the patient, and the stability of the fracture, the quality of the bones, and the associating surgical and medical problems (1,2).

For the elderly patients with good general health status, good bone quality, and appropriate fracture type, morbidity and mortality still increases by the unsuccessful fixation of the internal fixation devices, injury to the joint by drilling the collum or caput of the femur, high infection rate, and late mobilization (3).

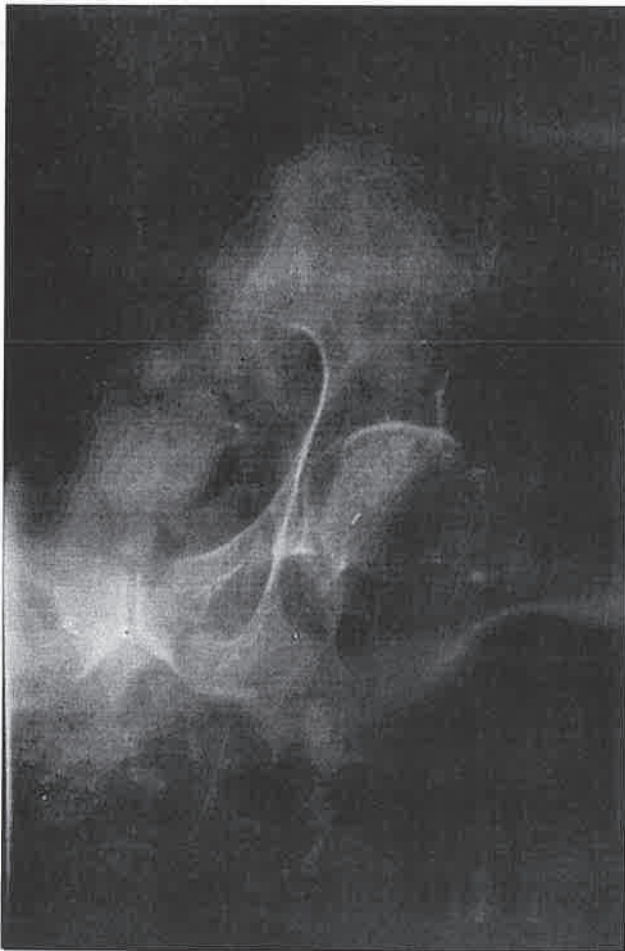


Fig. 1 A: Preoperative radiograph of trochanteric fracture with an intact trochanter minor.



Fig. 1 B: Postoperative radiograph of a the case; bipolar hemiarthroplasty applied.

Major internal fixation devices, used for the fractures of this region, are; rigid plate screws (Jewett, McLaughlin, etc.), sliding compression plates (Richard, AO Synthes), compression screws (Sliding hip screw), osteotomy and plate fixation (Dimon-Hughston, Sarmiento), intramedullary nailing (Condylo-cephalic types, Gamma screw), and bone cement. In clinical applications these implants are observed to give unsatisfactory results for weak and porotic bones (4,5,6).

Conflicts about usage of intramedullary nailing, like with flexible Ender nail or Condylo-cephalic nail, for the unstable intertrochanteric and subtrochanteric fractures are still going on. Many authors report unsatisfactory results. Although Kemf et al. states that migration of elastic implants can be prevented by the combination of distal locking screws, cerclage wires, and bone cement application techniques, early mobilization arises many mechanical problems (7).

Another alternative for the intramedullary nailing devices is the Zickel nail. It gives good results especially at the subtrochanteric fractures. But, again, difficulties are encountered in elderly patients who already have problems in being mobilized (8).

Kyle et al had a nail complication rate of 6.8% for the 74 unstable trochanteric fracture cases treated by osteosynthesis (9). Laros and Moore reported their complication rates, belonging to the fixation of comminuted trochanteric fractures, as 25% (10). Hayward et al observed 35% nail plate related, and 37.5% Ender nail related complications in their 182 intertrochanteric fracture cases (11).

Besides these, Rosenfeld et al. had applied Lienbach prosthesis to 38 patients with intertrochanteric fractures and obtained good results in 33 of them (12). Again, 88% excellent results were observed by Stern and Goldstein in their Lienbach prosthesis applied 29 intertrochanteric fracture series (13).

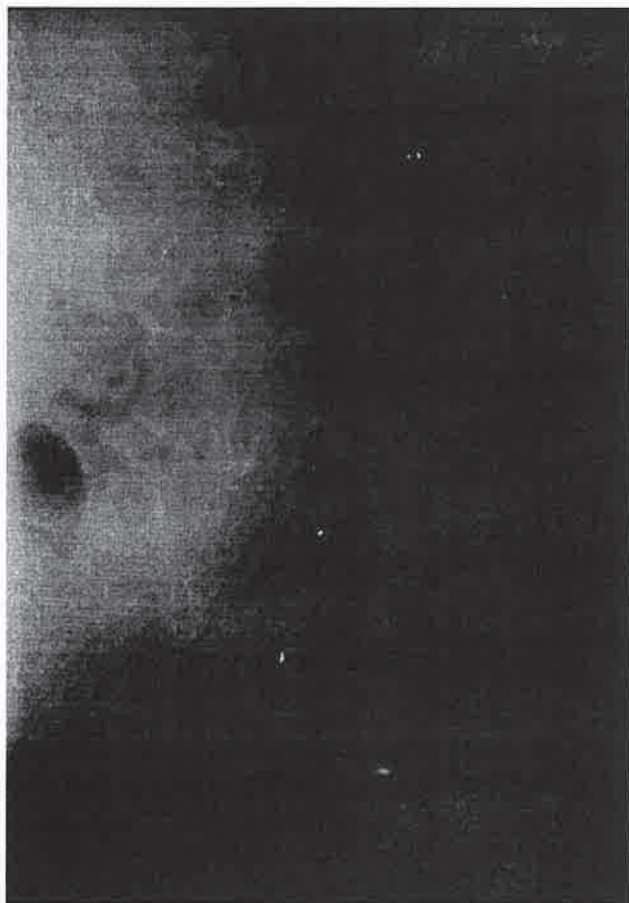


Fig. 2 A: Preoperative radiograph of a trochanteric fracture. Trochanter minor is also fractured leaving bone devoid of medial support.



Fig. 2 B: Postoperative radiograph of the same case; Head-neck type bipolar hemiarthroplasty applied.

Among the internal fixation applied patients approximately 60% encounter technical insufficiencies while more than a third necessitate revision. Continuous hip pain is another frequent and important problem. These are the reasons why many orthopedic surgeons prefer primary arthroplasty for elderly patients. Authors like D'Arcy and Devas, Evarts, and Tronzo were the first ones to apply endoprosthesis to elderly patients with trochanteric fractures. They have reported 30% decrease in hospitalization time and less complications with early mobilization advantages over internal fixation (14,15,16).

Broos et al have made a long prospective study comparing various osteosynthesis types and endoprosthesis applications (17). They have analyzed hip fracture cases treated by various osteosynthesis techniques between 1974 and 1977, and cases treated by endoprosthesis or total hip replacement between 1983

and 1988. While there has been no meaningful difference in the mortality rate between these two groups, endoprosthesis applied cases were apparently superior to the other ones when assessed in the point of pain and functional status after the first year. Broos et al stated that endoprosthesis should be the treatment of choice for the intracapsular fractures of the elderly patients.

Having many advantages, endoprosthesis have complications like acetabular erosion, stem loosening, dislocation, and myositis ossificans. Acetabular erosion, being a problem especially in one-piece (unipolar) prostheses, is seen approximately in 10 to 15% of the cases. Loosening of the stem is reported to be observed in 16 to 48% of the cases. We have seen acetabular erosion in four (13.3%) of our patients. For the three of these cases unipolar and for the other one bipolar prostheses were used (18). Shear forces have be-

en eliminated for the first time by the bipolar prosthesis developed by Bateman- Averill, and by this way, a hip, functioning better, painless, causing less harm to acetabulum, and having decreased stem insufficiency rates, was obtained (19). Bipolar prostheses are more expensive due to their complex constructions. They should be preferred less when survival time and expectations from life quality are limited (20,21,22,23).

Long term follow-up for elderly patients is a difficult task to perform. Some of the patients die in the hospital, while most of the rest, having decreased functional, physical, and mental capacities, die in the postoperative first year. Six of our patients died in the first 12 months following operation.

Most our patients, 75 years or older, had major medical disorders associating their fractures. Some of the patients were hospitalized for long times before being ready for surgical treatment. The mean time between admission to the hospital and the operation were 6 days. This is high compared to the literature and was caused by the associating medical problems of the patients and the economical insufficiencies.

Exitus rates within the hospitalized period is reported between 3 to 10%. In our series 4 patients (8.3%) died in the early postoperative period, and this correlates with the literature. Reasons of death were decompensated cardiac failure and pulmonary embolism.

6 (12.5%) of our patients died in the first 12 months postoperative period (24).

Mean hospitalization time was 13.6 days. Many different results have been postulated about this subject. The hospitalization period closely correlates with the associating medical disorders of the patient.

As complications, we have encountered no dislocation of the prosthesis in the postoperative or the follow-up periods. Various results have been reported for the dislocation rate. Inappropriate prosthesis size, unnoticed difference in the length of the extremities, or wide femoral component were blamed to be the causes of dislocation. We did not have any deep tissue infections due to routine application of appropriate antibiotic prophylaxis. Since we were not able to have long term follow-ups, stem loosening rate was not defined. Although prophylactic treatment against thromboembolic disorders were applied to all of the patients, gross pulmonary emboli developed in two cases, and they have died in the early postoperative period (25).

We have justified the reasons of not being able to do long follow-ups as, patients being old and not having anyone to look after, having difficulties in coming to the hospital for controls, having economical problems, and above all exitus rates being high in this age group.

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RECOMBINANT HUMAN ERYTHROPOIETIN ADMINISTRATION IN OPEN HEART SURGERY

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Atilla Aral* • Yeşim Batislam** • Ümit Özyurda* • Hakkı Akalın*

SUMMARY

Despite the recent developments in blood conservation techniques, postoperative anemia and multiple blood transfusions are still important problems in cardiac surgery. Autologous donation and reusing of shed blood are the frequently used techniques to reduce banked blood transfusion. During the last few years there have been some reports indicating that multiple "Recombinant Human Erythropoietin (r-Hu EPO)" infusions starting at least two weeks before operation, induced erythropoiesis.

We aimed to reduce the risk of adverse reactions of high doses of r-Hu EPO and the period of hospitalisation. Thus we investigated the effect of erythropoietin infusion with single low dose (100 IU/kg) on erythropoiesis administered one week before surgery.

Twentyfive patients received r-Hu EPO and 28 patients formed the control group. In the r-Hu EPO group the mean hemoglobin value had increased significantly on the morning of operation. It was also significantly higher than it was in the control group (14.5 ± 0.52 gr/dl in the EPO group and 12.4 ± 0.65 in the control group) ($p < 0.05$). In the postoperative period the Hb. levels in both groups were kept over 8.5 gr/dl by homologous transfusion. In order to maintain this, 330 ± 33 ml. homologous transfusion was required in the EPO group whereas it was 680 ± 75 ml. in the control group ($p < 0.01$). No adverse reactions or undesirable effects were seen with of the r-Hu EPO treatment and we conclude that; r-Hu EPO induces erythropoiesis rapidly even it is used with a low single dose before surgery, therefore this method can be accepted as one of the methods aiming to reduce homologous blood transfusion.

Key Words: Recombinant Human Erythropoietin, Open heart surgery, Homologous blood transfusion

Anemia is one of the main problems that is seen after open heart surgery. Activation of the contact coagulation factors during extracorporeal circulation causes activation of the complex fibrinolytic system (1,2,3). Studies have shown that there are major reductions in the plasma levels of almost all factors but most of these changes are hemodilutional (4,5). Moreover cardiopulmonary bypass shortens the erythrocyte life by increasing its fragility (6,7,8). Because of the reasons mentioned above, despite the meticulous surgical hemostasis, blood loss can be so great as to cause anemia. For the treatment of this anemia blood and blood products are used which also brings a lot of problems such as transfusion reactions, volume overload, infections, etc...(9,10,11)

There are many reports on blood salvage, diminishing blood loss, the materials which are used instead of whole blood and on the drugs which induces

erythropoiesis. Autologous donation is most preferred method to replace blood loss and fresh platelets and coagulation factors, however anemia is a common problem in open heart surgery despite autologous donation.

In 1977, Miyake and his colleague (12) isolated erythropoietin hormone that induces erythropoiesis and in 1985, Jacob and Linn (13) had produced for the first time Recombinant Human Erythropoietin (r-Hu EPO) by using recombinant DNA technology and this had become a great development for the treatment of the anemia caused by the lack of erythropoiesis. In the present r-Hu EPO has become the main agent in treating the anemia caused by reduced erythropoiesis that is seen in chronic renal insufficiency and some hemotologic diseases (14,15).

In this study we tried to investigate the effect of low and single dose (100 IU/kg) r-Hu EPO on erythropoiesis using it one week before surgery.

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MATERIAL AND METHOD

This study included fiftythree patients who were randomly chosen from those waiting for elective CABG surgery. Twentyeight of them formed the control group. The remaining twentyfive patients received 100 IU/kg recombinant human erythropoietin intravenously seven days before operation (r-Hu EPO group). Hemotologic system analysis of the patients were normal. None of these patients had any disease or addiction (drug abuse, alcohol abuse, corticosteroid treatment, etc...) that might possibly effect bone marrow response. The characteristics of the both groups is shown on Table I. There is no statistical difference between two groups about their preoperative characteristics.

The complete blood counts, routine serum chemical parameters, serum iron, iron binding capacity values and serum erythropoietin levels were measured on admission, on the day before surgery, on first postoperative day, one week after surgery. All patients donated 400 ml. of blood on the operation morning. This blood was conserved and given back to the patients after protamine. All patients underwent succesful coronary bypass surgery without major complications. All operations were carried out with cardiopulmonary bypass using Sci Med membrane oxygenator, cold potassium cardioplegia and moderate hypothermia. Intraoperative autotransfusion systems (Cell Saver) were used to minimize homologous blood transfusion. Two large bored, silicone coated thoracic drains were placed in mediastinum, thoracic cavities were drained separately if required. Postoperative drainages were collected to underwater drainage system. Patients were ventilated with volume controlled ventilators for at least 4 hours (at most 17 hours). Five to 10 mm Hg PEEP was used unless hemodynamically unstability was present. In the postoperative period hematocrit levels

of the patients were kept over 28 % (8.5 gr/dl Hb) by administration blood.

All data were expressed as the mean \pm standart deviation. The statistical evaluation of the results have been made according to the students "t" test and test for two proportions from independent groups.

RESULTS

All patients underwent successful coronary bypass surgery without major complications. They have completed their postoperative course and they have been discharged on the 8 th to 11 th postoperative days. Upon admission to the hospital there was no significant difference in hemoglobin values between two groups (Control: 12.5 ± 0.51 , r-Hu EPO: 12.1 ± 0.38 gr/dl) ($P > 0.05$). After r-Hu EPO administration hemoglobin values elevated significantly (14.5 ± 0.52 gr/dl) in the r-Hu EPO group, and this finding was significantly different from the control group ($p < 0.05$). Therefore, the preoperative hemoglobin values were higher in the r-Hu EPO group than the control group. The hemoglobin values measured 24 hours postoperatively were not significantly different between the two groups (Control: 10.3 ± 0.60 , r-Hu EPO: 11.2 ± 0.72 gr/dl) ($p > 0.05$). But one should know that in our intensive care unit, hemoglobin values of the patients measured every hour until 24 hour postoperatively and the patients with lower hemoglobin values received homologue blood transfusion. There is no significant difference between the hemoglobin values of the two groups at the end of first week postoperatively (Control: 11.5 ± 0.58 , r-Hu EPO: 12.1 ± 0.62 gr/dl) ($P > 0.05$).

In the r-Hu EPO group the patients received 330 ± 43 ml. homologue blood transfusion during the period of operation time to discharge from the hospital. The control group received 680 ± 75 ml. homologue

Table I: Characteristics of patients

	Control	r-Hu EPO
Number of patients (n)	28	25
Age(yr): Mean	66.2 ± 4.7	59.8 ± 5.4
Minimum	38	36
Maximum	77	80
Sex: Male	17	16
Female	11	9
Mean days of hospitalisation	9.1 ± 0.6	9.7 ± 0.8
Cross-clamp time (min)	51.2 ± 6.2	47.7 ± 5.9
Total operative time (min)	192.6 ± 11.4	211.6 ± 14.6
Revascularised coronary arteries (n)	2.7 ± 0.4	3.2 ± 0.5

blood during the same period. The difference between the two group was found to be significant ($P<0.01$).

There was no significant difference in the reticulocyte values between both groups as they were hospitalized (Control: 55 ± 9.80 , r-Hu EPO: 51 ± 7.01) ($p>0.05$). The patients who received r-Hu EPO had significantly higher reticulocyte values after the r-Hu EPO administration than the control group (Control: 53 ± 8.20 , r-Hu EPO: 135 ± 15.07) ($p<0.01$). Even though the reticulocyte values increased a little bit in the control group 24 hours postoperatively, the difference in these values between both group was found to be significant (Control: 68 ± 8.06 , r-Hu EPO: 126 ± 9.35) ($p<0.01$). The reticulocyte values measured one week postoperatively decreased to the levels that was measured during the hospitalisation in the r-Hu EPO group and increased slightly in the control group. Therefore no significant difference between the both groups was observed at the end of one week (Control: 88 ± 9.99 , r-Hu EPO: 75 ± 10.35) ($p>0.05$), but these reticulocyte levels of the both group was significantly higher than the hospitalisation levels ($p<0.05$).

There was no statistically significant difference in the serum erythropoietin values between the two groups ($p>0.05$). But the serum erythropoietin values of the control group was slightly higher than preoperative values and this elevation was not statistically significant ($p<0.05$). The brevity of the elimination half - life of r-Hu EPO (4 hours) did not cause any change in the serum erythropoietin levels of the patients.

All preoperative and postoperative serum iron and iron binding capacity values were not significantly different between two groups ($p>0.05$). All data is shown on Table 2.

During the postoperative first 24 hour period, in the control group 470 ± 45 ml. drainage, and in the r-Hu EPO group 430 ± 40 ml. drainage was observed.

There was no significant difference in the drainage fluid values between the two group ($p>0.05$).

During the study blood smears were done for the detection of the possible hemotologic disturbances at certain periods and no considerable property was determined.

DISCUSSION

It was observed that the patients who received r-Hu EPO had induced erythropoiesis in a short period of time and had marked increase in their hemoglobin values. The hemoglobin values of the r-Hu EPO group was 12.1 ± 0.38 gr/dl as they were hospitalized and seven days after r-Hu EPO administration, on the operation day the values increased to 14.5 ± 0.52 gr/dl. The difference between these values appeared to be statistically significant ($p<0.01$). The hemoglobin values of the control group was 12.4 ± 0.65 gr/dl on the day of operation. The differences of the hemoglobin values between the two group was statistically significant ($p<0.05$). Therefore the patients in the r-Hu EPO group undergo operation with higher hemoglobin values compared to the control group.

During the period between the operation and the discharge from the hospital, the patients in the r-Hu EPO group received 330 ± 33 ml. homologue blood transfusion. The patients in the control group were transfused 680 ± 75 ml. homologue blood at the same period. The difference between two groups were statistically significant ($p<0.01$). Therefore it was observed that the requirements of blood products for the erythropoietin group is less than the control group patients.

Studies about r-Hu-EPO administration prior to open heart surgery were reported in the literature (16,17,18,19). Moreover Watanabe and his colleagues

Table II: Hematologic values of both group before and after r-Hu EPO administration

	ADMISSION			OP. MORNING			POSTOPERATIVE 1. DAY			POSTOPERATIVE 7. DAY		
	Control	r-Hu EPO	P Val.	Control	r-Hu EPO	P Val.	Control	r-Hu EPO	P Val.	Control	r-Hu EPO	P Val.
Hb. levels	12.5 ± 0.51	12.1 ± 0.38	>0.05	12.4 ± 0.65	14.5 ± 0.52	<0.05	10.3 ± 0.6	11.2 ± 0.72	>0.05	11.5 ± 0.58	12.1 ± 0.62	>0.05
Reticul. count	55 ± 9.80	51 ± 7.01	>0.05	53 ± 8.20	135 ± 15.07	<0.01	68 ± 8.06	126 ± 9.35	<0.01	88.0 ± 9.99	75 ± 10.35	>0.05
Eryth. levels	10.4 ± 1.21	9.3 ± 1.50	>0.05	9.6 ± 1.72	12.1 ± 3.30	>0.05	4.7 ± 1.66	6.8 ± 1.82	>0.05	10.8 ± 2.19	8.9 ± 2.56	>0.05
Se. Iron levels	95 ± 11.44	101 ± 15.8	>0.05	120 ± 10.71	106 ± 12.46	>0.05	104 ± 7.18	98 ± 9.62	>0.05	101 ± 14.2	110 ± 13.16	>0.05
Se. Iron Bin. Cap.	336 ± 41.4	308 ± 32.6	>0.05	301 ± 27.6	320 ± 35.6	>0.05	316 ± 39.0	333 ± 31.6	>0.05	296 ± 32.6	317 ± 29.8	>0.05

reported the administration of the r-Hu EPO in the following week after the operation, in addition to preoperative usage (20). Also there are reports about administration of r-Hu EPO in multiple doses, but this has the disadvantage of overstay in hospital. In all these studies, hemoglobin values showed marked increase, and the requirement for blood and blood products markedly decreased.

r-Hu EPO treatment have hypertension, deep venous thrombosis, hypercalemia, flu-like syndrom and headache like side effects (21,22). But in our study we

did not observe any complications due to administration of r-Hu EPO. We think that low dose r-Hu EPO administration might play a role to avoid complications.

Blood and blood products transfusions may results many adverse effects such as transfusion reactions, volume overloading or infections. Therefore we believe that by giving 100 IU/kg single dose of r-Hu EPO preoperatively to the patients, the requirement of blood and blood products during surgery and postoperative period will markedly decrease.

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A CASE OF PENILE METASTASE

Levent Aydoğanlı* • M.Murat Başar* • Sevil Günçe** • Halil Başar* • Selda Seçkin**

SUMMARY

A 64-year-old man with penile metastatic tumor was presented. The clinical features and diagnostic criteria were reviewed.

Key Words: Neoplasm metastasis, Penile neoplasm

Metastatic tumors of the penis are rare. By 1992, 277 cases had been reported in the literature (1). We report a case with poor prognosis after first diagnosis.

CASE REPORT

A 64-year-old male patient was suffering from a painful nodule of the penis. He was diagnosed as having transitional cell Ca. of the bladder (grade -III) in July- 1995. He was treated with Transurethral Resection (TUR) and radiotherapy because he refused the radical cystectomy. After one year, he noticed a nodule on the penile shaft. This mass was getting greater, pain had started one week ago. Examination confirmed a hard nodule on the dorsal surface of the penis and localized glans and penile shaft, a slightly hypertrophic prostate and bilateral hydrocele (Figure 1). Other systems were found normal.

Laboratory findings were within remarkable limits; Prostate Specific Antigen (PSA) was 0.1 ng/ml, and PA chest graphy was normal. The abdominopelvic ultrasonography showed left hydronephrotic atrophic kidney and exophytic mass with 26 mm size on the left wall of the bladder. There was a hypoechoic nodule on the glans and bilateral corpuscavernosum; its size was 37x47x13 mm on the penile ultrasonography. Abdominal tomography showed bladder tumor with perivezical and vesicular invasion on the left and bilateral hydrocele. On the penile tomography, there has a mass with central necrotic hypodens zone (Figure 2).

After these findings, incisional penile biopsy was performed. On the pathologic examination, microscopically, hazardly infiltrating solid tumor islands were seen within a dense fibrocollagenized stroma. The tumor was composed of cells with small pleomorphic, darkly staining nuclei and variable amount of elongated cytoplasm. The cytological features and arrangement of tumor cells within these islands were reminiscent of transitional cell carcinoma (Figure 3).

We decided to apply chemotherapy. One month later, he got worse and had dyspnea. On the control chest graphy, we evaluated pneumonia and lung metastasis (Figure 4). He was discharged under his relieved decision, and died one-week later.

DISCUSSION

Although the first cases of penile metastases were reported about 100 years ago by Eberth in 1870 and Newman in 1882, metastatic tumors of the penis are rare (2). About 277 cases has been reported in the literature (1). Whereas it is related with the time of primary tumor, it is more common in the 6 decades (37-85 years, mean age 63,3) (3).

The possible routes for metastases have been described by Paquin and Roland (2). Direct extension from neighbor organs, retrograde venous transplantation, retrograde lymphatic extension, direct arterial dissemination, implantation with instrumentation are routes of metastases (2,3). But , two or more routes of

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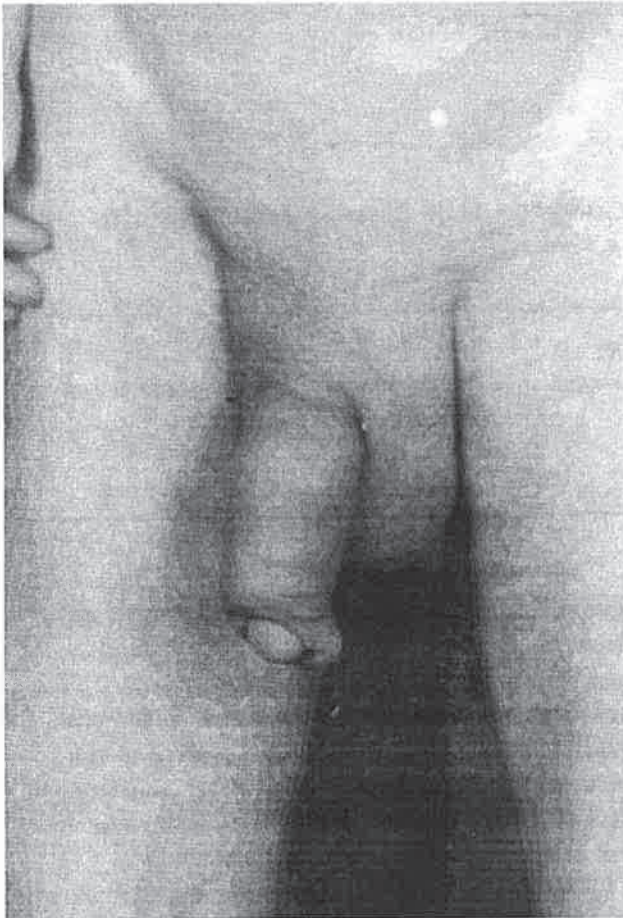


Fig. 1: A hard nodule on the dorsal surface of the penis and localized glans and penile shaft and bilateral hydrocele.

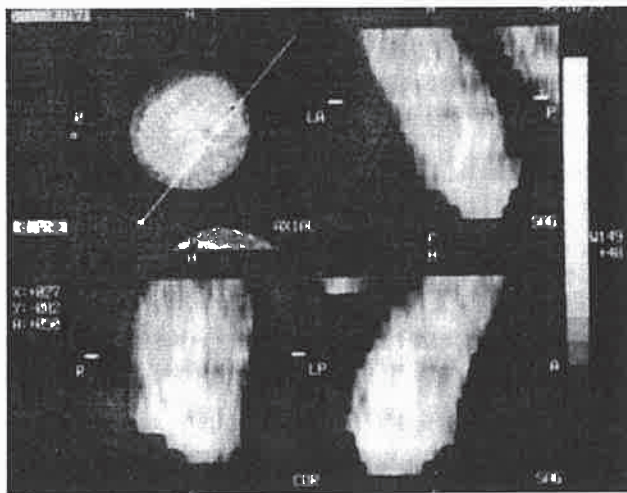


Fig. 2: Penile omography demonstrating a mass with central necrotic hypodense zone.

spread. Radiotherapy may increase the incidence of metastases to the penis from bladder (4).

The majority of the primary tumors are localized in the genitourinary tract (bladder (33.2%, prostate 30.3%, kidney 6.9%, testis 4% and urethra 0.4%) and the gastrointestinal system (rectosigmoid 16.2%, colon 1.1% and pancreas 0.7%). Lung (2.5%), nasopharynx (0.7%), bone (0.7%), skin (0.4%), lymphoma (0.4%) are less frequent localizations (1,5).

The main symptoms of metastatic penile tumors are nodular enlargement (%36-40), malign priapism (%30-38) and pain (%30). The nodule is localized on the penile shaft in 66%, on glans in 12% and on corpus spongiosum in 8%, and is solitary in 22% or multiple in the rest. Also, it has been reported as bilateral corpora cavernosa in 56%. However, symptomatology depends on the localization and the size of tumor (1,3).

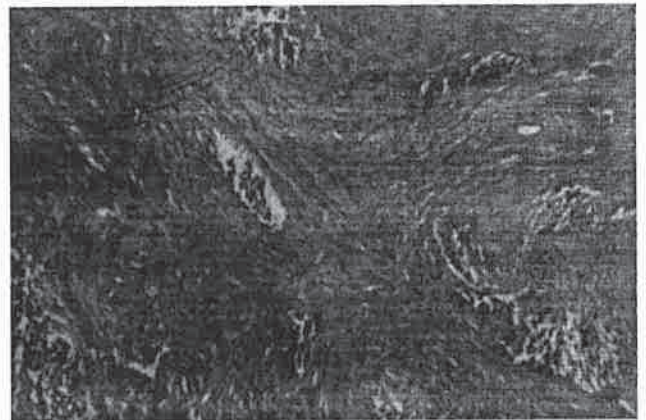


Fig. 3: Histology of the incisional biopsy specimen showing hazardly infiltrating solit tumor islands were seen with in a dense fibrocollagenized stroma.



Fig. 4: Pneumonia and multiple lung metastasis on chest graphy.

metastases may occur in a single case. Radiation therapy occult/closed the small lymphatic and venues and paved the way for retrograde venous or lymphatic

Multiple diagnostic tests have been described for the clinical diagnosis and staging of penile cancer. A penile lesion that does not respond to a short trial of conservative treatment requires biopsy. In the large lesion, the diagnosis is obtained by incisional biopsy; the specimen should be taken from the periphery of the lesion so that normal tissue may be included. Cavernosography has been advocated as a method of evaluating the corporal bodies. Ultrasonography is well suited for imaging of the penis, although little has been written on the use of it to evaluate penile cancers. MR and CT are better methods for the evaluation of penile lesions and lymphadenopathies (1). In our case, we did not perform cavernosography, because the lesion was clearly palpable and also the history of the patient was definitely clear.

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Treatment varies; local excision, total amputation, radiotherapy and chemotherapy have been suggested. But, the response is poor, and survival has been reported 6-112 weeks (3,4). The metastatic penile tumors originating from the genitourinary tract, have a worse prognosis than the others (4,5).

In our case, although there was a large unilateral and solitary nodule arising from the glans to the penile shaft, there was no urethral invasion. We thought that the metastatic route for this patient had two possible mechanisms incidentally: 1) Direct invasion because there was invasion on pelvic CT, and 2) retrograde lymphatic and venous extension because bilateral hydrocele occurred after radiotherapy. Also, this was a finding of destroyed lymphatic drainage. On the other hand, our case demonstrated a very poor prognosis after initial diagnosis, and showed multiple lung metastases in 1 month.

SIGNET RING CELL CARCINOMA OF THE BREAST (CASE REPORT)

Handan Özdemir* • Ayşe Sertçelik**

SUMMARY

In this article an unusual case of signet ring cell carcinoma (SRC Ca) of mammary is reported. The diagnosis was established using a mastectomy specimen from a 70-years old woman who was initially examined for left quadrant mass and left nipple discharge.

Many breast carcinomas irrespective of histologic type, do contain SRC's in small numbers (1). But they were never as frequent as in the case we reported (1). A confused entity signet ring cell (SRC) Ca of the breast have been seperated recently as an aggressive subtype of breast cancer, distinct from mucinous (colloid) carcinomas (2,3,4).

The distinctive clinical and pathologic features of SRC ca and because of their vastly different prognoses (2,3,4), warrant seperation of this group of tumors from other forms of breast ca.

Key Words: Signet Ring Cell, Mammary, Carcinoma, Breast

CASE REPORT

A 70-years-old female was admitted to the hospital with a four -month history of left upper outer quadrant mass with intermittant bloody discharge from the nipple. On her physical examination an irregular hard, palpable, poorly defined mass ranging from 4 to 5 cm in greatest dimension was encountered in the upper outer quadrant of left mammary. The nipple was hard with palpation. Fine needle aspiration was applied to the mass.

The final report of the cytopathologic specimen showed infiltrating ductal carcinoma.

According to this diagnosis a modified radical mastectomy was succesfully performed.

Gross pathologic features reflect the clinical presentation. Lesion is poorly circumscribed, 6x5x3 cm lobulated tan-white, relatively firm and homogeneous in consistency. Macroscopically the nipple was firm to palpation and 35 lymph nodes were obtained from axilla.

Microscopically the tumor consist of anaplastic duct lining cells disposed in cords and solid nests. The neoplastic cells diffusely infiltrated the fibrofatty tissue. High power fields containing more than 20 SRC

were identified. SRC's between these neoplastic cells were characterized by a clear cytoplasm, containing mucin and a crecentric nucleus displaced toward one end of the cell (Fig 1).

Intradermal spread of malignant cells from an underlying invasive carcinoma was observed in the nipple (Fig 2). The patient had axillary lymph nodal metastases with a 10/35 positive lymph nodes.

Stains for mucin, including PAS and mucicarmine were strongly positive in the cytoplasm of the SRC's in both the primary lesion and in the lymph nodes. The immunohistochemical staining of the specimen for estrogen receptor protein was moderately (++) positive.

The final report of the pathologic specimen showed infiltrating ductal ca with sigret ring cell component.

DISCUSSION

With the increasing use of conservative surgery and radiotherapy it is no longer sufficient for a pathologist merely to determine whether a breast excision specimen contains carcinoma cells. Certain histologic features of the primary tumor are considered by clini-

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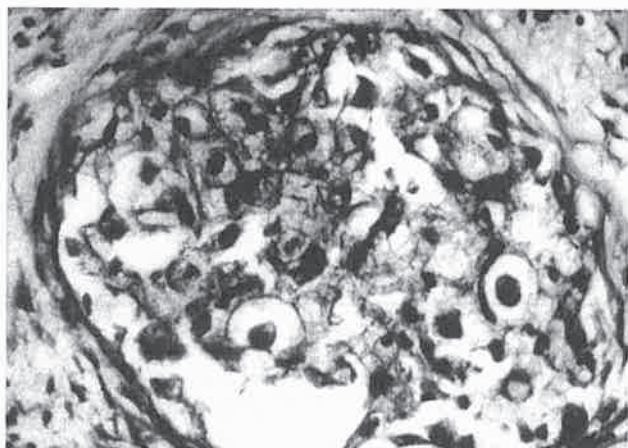


Fig. 1: H&E x 400 Signet ring cells characterized by a clear cytoplasm, containing mucin and crescentic nucleus displaced toward one end of the cell.

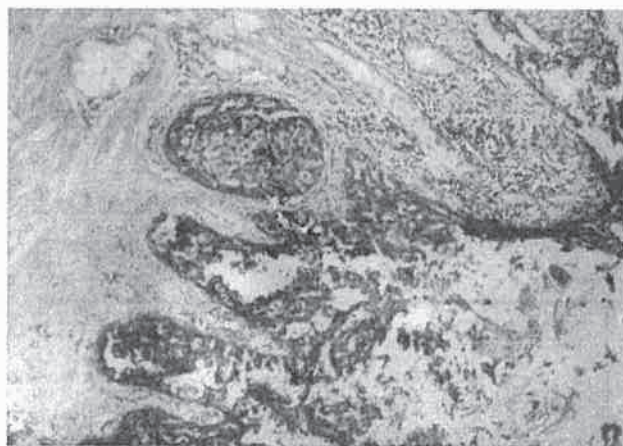


Fig. 2: H&E x100 Intradermal spread of malignant cells from underlying invasive carcinoma (pagetoid spread).

cians in planning appropriate local and systemic therapy for patients with breast cancer.

Several microscopic features of invasive breast cancers have been reported to be associated with an increased risk of breast tumor recurrence after conservative surgery and radiotherapy. These include high histologic grade, tumor necrosis, lymphatic and vessel invasion (2,5). In addition possible association of the SRC morphology with one of other specific histologic types of mammary carcinoma seems quite important. Because recent studies have indicated that the extent and distribution of SRC's in association with an invasive carcinoma is important in determining the risk of local recurrence and metastases. According to these authors SRC carcinoma of the breast must be separated as an aggressive subtype of breast cancer distinct from mucinous (colloid) carcinomas (1,3,4,6).

The tumors which were composed of SRC's can manifest as a pure lesion or as a mixed type carcinoma (3). Cases of SRC carcinoma were considered "pure" when no coexisting histologic type could be identified (3,7). When a second histologic pattern such as ductal, colloid or lobular carcinoma was also present, the lesion was designated "mixed" (3,8). The tumors which were composed purely of SRC are rare and only two pure SRC carcinoma were reported (7). Mixed type SRC carcinoma accounts for 2 % (4) to 4 % (9) of all mammary cancers.

The criteria for the diagnosis of SRC carcinoma varies. SRC carcinoma mammary was firstly described in 1941 by Saphir as an extensive collection of intracellular mucin in the form of SRC in large area (10). The term SRC have used to refer to any cell whose

nucleus is reduced to a crescent, bounding one portion of the cytoplasm. The cytoplasm of these cells contained a well defined globule of mucicarmophilic material (10,11).

The cases were designated SRC carcinoma when the tumors contained foci with more than 20 neoplastic cells with mucicarmophilic, PAS (+) cytoplasmic vacuoles per high power field (3). In order to give a definitive diagnosis, the cytoplasmic vacuoles within the neoplastic cells must stain positively with mucicarmine. Distortion of the nucleus into a crescent shape was not a prerequisite for this diagnosis (1,3).

Still there are some authors which has not recognized SRC carcinoma as a specific entity (1,9). These authors described SRC carcinoma as a subgroup of mucinous carcinoma (5,10) and as a variant of lobular carcinoma (1,11,12). As a matter of fact that, these are distinctly different forms of mammary carcinoma. To avoid confusion between colloid carcinoma and SRC carcinoma, mucin histochemistry must be done. In colloid carcinoma the mucin accumulations are characteristically much more extracellular, whereas in SRC carcinoma the accumulation is intracytoplasmic (1,3). In addition colloid carcinoma has a less aggressive natural history, with lesser axillary lymph nodal metastases and longer survival (2,5,7).

Ductal carcinoma with a SRC component comprised 2 % of all mammary cancers (3). As in the case we presenting, infiltrating ductular carcinoma composed of 10 % or more SRC's were more likely to show axillary lymph nodal metastases and recurrence (3). According to papers which had been reported in re-

cent years it becomes obvious that the presence of SRC's within a carcinoma appears to impart a more aggressive behaviour to the lesion (3,4,6,9).

In conclusion; SRC carcinoma occurs as a pure lesion or in association with infiltrating lobular, ductu-

lar or colloid carcinoma. Thus it is a more aggressive variant of mammary carcinoma with a poorer prognosis, especially in its purest form. So SRC carcinoma must separate from other types of mammary cancers and accepted as a specific entity.

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APPENDICITIS IN FEMORAL HERNIA (CASE REPORT)

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SUMMARY

Herniation of the appendix into the femoral hernia sac is unusual. An 65 years old woman presented with acute appendicitis in a right strangulated femoral hernia. The hernia was diagnosed preoperatively, but the gangrenous appendix was found only at operation. The symptoms of appendicitis are over shadowed by findings of the incarcerated femoral hernia. There were no abdominal signs or symptoms. Treatment is controversial, but appendectomy and Cooper ligament herniorrhaphy has definite advantages.

Key Words: Acute appendicitis, Femoral hernia,, Preperitoneal approach

The first successful appendectomy was performed through an inguinal hernia sac by Amyand in 1736. The first case of a femoral hernia with appendicitis was reported by DeGarengot in 1731. Herniation of the appendix into the femoral hernia sac is rarer still. There are only 63 reported cases of the latter as much as 1988 in the literature (1).

An acutely perforated appendicitis in a femoral hernia is almost never diagnosed before to surgery. Most often the diagnosis of this clinic situation is incarcerated or strangulated hernia (2). A rare case is reported of a woman who presented with pain in the right femoral region and palpable crepitus and who was found to have a perforated appendicitis.

CASE REPORT

An 65-year-old woman presented with a 3-day history of increasing pain, swelling and redness of right femoral area, with intermittent fever. Despite analgesic, the pain increased. The right leg became swollen on examination. There was a tender, 4x6 cm nonreducible mass in the right groin. The skin overlying the mass was erythematous and fluctuant. There were no abdominal signs or symptoms. Bowel sounds

were present. Her temperature was 37.5 °C, blood pressure 140/70 mmHg (her medical history included hypertension, she was taking furosemide and beta blocking agent), pulse rate 82 beats/min and respiratory rate 20/min.

The patient's hemoglobin level was 12.5 g/dL and leukocyte count was 10.000/mm³ with a left shift. Her blood glucose level was 125 mg/dL. Blood chemistry screen and chest radiography were within normal limits. X-ray plain films of abdomen appeared normal, not demonstrate a faecalith in the area of the appendix. Ultrasound have been used in the evaluation of patient. Ultrasound criteria for the diagnosis was not visualized.

Intravenous fluids and antibiotics (cephalosporin 2gr/per a day and aminoglycosid 160 mg/per a day) were administered. The preoperative diagnosis was an incarcerated femoral hernia. The patient was taken to the operating room. A right groin incision was made. A preperitoneal surgical approach was used. A femoral hernia was identified. There was an incarcerated femoral hernia with a perforated gangrenous appendix within the hernia sac. (Figure 1)

The sac contained a perforated appendix with 10 ml of pus. The femoral canal was irrigated with 0.9%

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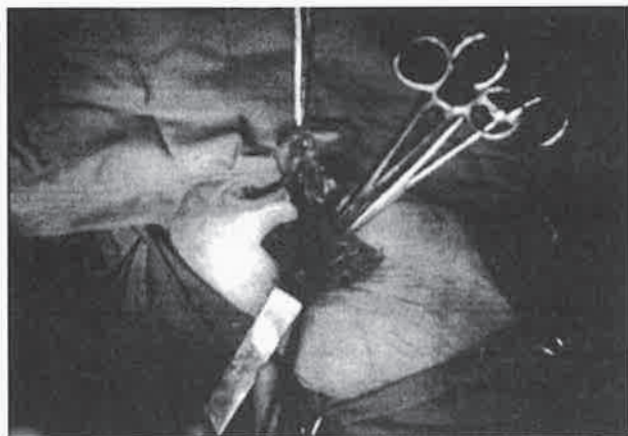


Fig. 1: There was an incarcerated femoral hernia with a perforated gangrenous appendix within the hernia sac.

serum saline. The peritoneum was opened and appendectomy was performed. The peritoneum was closed and Cooper ligament herniorrhaphy was performed. A hemovac drain was placed in the preperitoneal space and the patient was continued with antibiotics. The patient did well and was discharged nine days after surgery.

DISCUSSION

An inflamed appendix is a less common finding, with 63 reported cases (1). Although the frequency of acute appendicitis in femoral hernias is unknown, an estimated 0.13% of cases of acute appendicitis occur in various external hernia sacs (3,4). An incarcerated femoral hernia can contain any of several intraabdominal organs (omentum, small bowel, colon, stomach, Meckel diverticulum etc.). In our case, it contained a perforated gangrenous appendicitis.

It is often impossible to differentiate appendicitis in the femoral hernia sac from incarcerated and strangulated femoral hernia by physical examination alone, but accurate history will generally solve the dilemma (2,5). Acute appendicitis in a femoral hernia often occurs in women in their 6th decades with a right-sided femoral hernia (2). The signs and symptoms usually relate to the gastrointestinal tract and the skin overlying the hernia (6). Our case have a erythematous skin overlying the mass, but there were no abdominal signs or symptoms.

Laboratory examinations are rarely helpful in the diagnosis of appendicitis (6). Likewise, in our case, laboratory findings can not help. Ultrasound have been used in the evaluation of patients with suspected appendicitis. Sensivity rates of 75 per cent and specificity rates of 100 per cent have been reported. But, ultrasound can not been used in the evaluation of patients with appendicitis in the femoral hernia sac (6).

Blood chemistry screen and chest radiography were within normal limits (6). In our case, these results were normal.

Fever and leukocytosis are a late physical finding in appendicitis. Before perforation, body temperature is usually no more than 39 to 39.5 °C, but with perforation may rise to 40 to 41 °C (6). In our case, body temperature was 37.5 °C, leukocyte was 10.000/mm³. These situation may be explained by a tight femoral neck which prevents the spread of pus throughout the abdomen (2).

Gangrenous perforated appendicitis in a strangulated femoral hernia is thought to be caused by constriction of the lumen of appendix by the neck of the femoral hernial sac. Subsequently, this situation leads to inflammation and gangrene of the appendix (7). In our case, the infection spread into right femoral hernia sac but no femoral region.

Treatment is controversial. The management of non-perforated appendicitis is surgical removal (8). The risk of perforation is low in the first 24 hours of symptomatic appendicitis (6). Watkins proposed initial drainage and interval appendectomy and hernia repair (1). Voitk et al. performed incision and concurrent with appendectomy and hernia repair (9). Cuotolo and colleagues performed incision and drainage, followed three days later by celiotomy, appendectomy and hernia repair (10). A preperitoneal surgical approach can be used appendectomy together Cooper ligament herniorrhaphy can be performed and then a drain can be placed preperitoneal area (2). In our case, we were used this surgical approach.

In conclusion, an acutely appendicitis into the femoral hernia sac is unusual. The treatment of choice is an appendectomy with a preperitoneal hernia repair and the preperitoneal approach minimizes contamination and potentially spares the patient a second procedure.

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