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EFFECTS OF FINASTERIDE - A 5α-REDUCTASE INHIBITOR - ON HIRSUTISMUS AND HORMONAL LEVELS IN WOMEN: A PRELIMINARY REPORT *

A. Nuri Kamel** • Sevim Güllü** • Vedia (Cesur) Tonyukuk** • Nilgün Başkal** • Ali Rıza Uysal** • Gürbüz Erdoğan**

SUMMARY

Increased activity of 5α-reductase (5α-R) in skin is considered to play a role on hirsutismus in women. In the present study, the effects of finasteride - a 5α-R inhibitor- on hair growth and on serum hormone levels were evaluated before and during the treatment. The degree of hirsutismus was assessed according to the Ferriman Gallwey's score. Eight patients with idiopathic hirsutismus, and two patients with polycystic ovarian disease, ages between 16-33, were given 5 mg finasteride once a daily for three months. Serum hormonal evaluations were done basally, and periodically during treatment. A reduction in serum total testosterone was observed at the third month ($p<0.05$). Serum cortisol levels showed a transient decrease at the first month ($p<0.01$). No other significant change was observed in other hormonal levels. Ferriman Gallwey score reduced from 19.2±4.4 to 14.8±3.9 ($p=0.005$). No adverse effect was observed. These preliminary results indicate that, finasteride is a safe and effective drug in the treatment of hirsutism in women.

Key Words: *Finasteride, Hirsutism*

Hirsutism is the growth of terminal hair, in male pattern, in women(2,3,8,14) Dihydrotestosterone is supposed to be the androgen, that is responsible for the androgen dependent hair growth(14). An increased activity of 5α-reductase (5α-R), which converts testosterone to its active metabolite dihydrotestosterone, was detected in the skin of hirsute women(9,11,17-19). Higher concentrations of 3α-androstanediol and its glucoronide conjugate, which are important metabolites of dihydrotestosterone in skin, were also found in plasma and/or urine of hirsute women(7,17,22). As women with congenital 5α-R deficiency show no clinical abnormality, an agent that selectively blocks 5α-R should give no harm to female patients, while decreasing androgen dependent hair growth.

Finasteride is a competitive 5α-R inhibitor, that was first developed for the treatment of benign prostatic hyperplasia in men (13,15,20,21). Recently, its use for hirsutism, was reported by some authors(5,10,23). These workers reported a significant decrease in hirsutism score within three to six months.

The aim of this study is to evaluate the effects of finasteride on hirsutism score and on hormonal levels in hirsute women.

PATIENTS AND METHODS

Ten patients, eight with idiopathic hirsutism and two with polycystic ovarian disease (POCD), between ages 16-33 yr with a mean age 23 yr were included to the study. Among patients, nine had regular menses and one patient with PCOD had oligo-hypomenorrhea. Body mass indexes ranged between 18.6 and 33 (kg/m^2, mean 24.4). The degree of hirsutism was determined by Ferriman-Gallwey score(4). The score was between 11-25. The women were warned to avoid pregnancies by using non-hormonal conception methods during treatment.

Serum samples for determination of FSH, LH, PRL, estradiol (E2), progesterone (P), 17α OH progesterone (17 OH P), DHEA-S, cortisol (F), ACTH, free testosteron (fT), total testosterone (TT), TSH, levels were taken at the early follicular phases of the

* This study was presented as a poster at the 8th Balkan Endocrinology Congress (Bursa, 1995).

** Department of Endocrinology and Metabolism, Faculty of Medicine, University of Ankara

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menstrual cycles, before and at the first and at the third months of the therapy.

After basal determinations, all women were given 5 mg of finasteride, once daily, via oral route. Clinically, hirsutism score evaluations according to Ferriman- Gallwey score, body weight and blood pressure measurements were done at each visit. Hepatic and renal functions, fasting and two hour postprandial plasma glucose levels, fasting total and high and low density lipoprotein cholesterol, triglyceride levels and haematologic tests were also followed during the study.

Hormonal determinations were done in dublicate with either RIA kits (Amerlex (UK) for E2, progesterone and cortisol, DSL (USA) for 17 OH P, DPC (USA) for fT, TT, and DHEA-S ICN Biomedical Inc. (USA) for ACTH) or IRMA Kits (Origon Diagnostica (Finland) for prolactin, Medgenix (Beligum) for FSH, LH and TSH).

Statistical analyzes were done by the Wilcoxon test and paired-t test.

RESULTS

Clinical Effects:

Neither significant side effects nor menstrual cycle irregularities were reported by the women while taking finasteride. Blood pressures remained stable during the treatment.

Hepatic and renal functions, lipid and glucose concentrations, haematologic profile showed no abnormality with the drug therapy.

Improvement in the hirsutism score was observed in all women, slightly in three, significantly in the other seven patients. Total score decreased from 19.2±4.4 to 14.8±3.9 (average 22.9%, p = 0.005) at the third month.

Hormonal effects:

Hormonal profile of the women before, at one month and at three months of the treatment were given in table I.

Serum total testosterone levels were found to be reduced according to the basal levels at the third month (51.8±26.1 ng/dL vs 76.1±34.9 ng/dL, p<0.05). Posttreatment mean free testosterone levels did not show any difference from baseline.

Mean basal cortisol level was 21.3±7.8 µg/dL, and decreased to 14.9±3.8 µg/dL after one mont (p<0.01), but returned to baseline level at the third month.

No changes in FSH and LH levels were observed during the treatment. ACTH, E2, P, 17 OH P, PRL, TSH, DHEA-S concentrations were also remained unchanged.

DISCUSSION

This study is planned to evaluate the effects of a 5α-reductase inhibitor (finasteride) on serum hor-

Table 1. Serum hormone concentrations before and during 5 mg/day finasteride treatment

Hormone	Basal	1 month	3 month
ACTH (pg/ml)	28.4 ± 31.7	22.2 ± 14.7	25.9 ± 13.2
F (µg/dl)	21.3 ± 7.8	14.9 ± 3.8*	19.7 ± 4.1
FSH (mlu/ml)	6.1 ± 2.5	4.6 ± 2.1	5.9 ± 2.4
LH (mlu/ml)	9 ± 4.9	5.5 ± 3.4	6.8 ± 5.2
E2 (pmol/L)	236 ± 267	210 ± 110	228 ± 319
P (ng/ml)	0.79 ± 0.48	0.77 ± 0.28	0.70 ± 0.42
17 OH P (ng/ml)	1.62 ± 0.97	1.39 ± 0.73	0.988 ± 0.31
DHEA-S (µg/dl)	410 ± 240	300 ± 131	335 ± 221
Total T (ng/dl)	76.1 ± 34.8	73.5 ± 36.2	51.8 ± 26.1#
Free T (pg/ml)	3.4 ± 1.7	3.4 ± 1.,6	3.1 ± 1.0
PRL (mlu/L)	211 ± 70	211 ± 71	235 ± 106
TSH (mlu/ml)	1.3 ± 0.9	1.7 ± 0.9	1.6 ± 0.5

Values are the mean ± SD
* p < 0.01 vs. basal value # p < 0.05 vs. basal value

F: Cortisol, E2 Estradiol, P: Progesterone, 17 OH P: 17α OH progesterone, T : Testosterone, PRL: Prolactin

monal levels, on non-hormonal parameters and on hirsutism score. Up to date, finasteride was mostly used for benign prostatic hyperplasia, in men, safely (13,15,20,21). Recently, the efficacy of the drug on excess hair growth in hirsute women was reported(5,10,23).

In the present study, with the chosen dosage (5 mg daily), we did not observe any adverse effect, either clinically or biochemically, in our patients. Plasma glucose, total cholesterol or HDL and LDL cholesterol, triglyceride levels were unaffected by finasteride.

As external genitalia abnormalities in male fetuses of the rats exposed to finasteride inutero was reported (1), all patients used non-hormonal contraception methods during the treatment. Although, we did not evaluate the ovulation in our patients, Moghetti et al showed the maintainance of the ovulatory menstrual cycles in their patients taking finasteride(10).

The degree of hirsutism, which was determined according to Ferriman- Gallwey score, decreased significantly at the third month with finasteride therapy. An average of 22.9% reduction in the score was observed with short term drug use. While, Fruzzetti et al. reported a 27.8% improvement in three months(5), Moghetti et al. observed nearly 50% reduction at sixth month(10). Wong et al. also reported a significant improvement in hirsutism score in their patients(23).

Serum gonadotropin levels did not show any difference from the baseline with the finasteride treatment in the present study, in agreement with the results of Fruzzetti et al, who also found no change in gonadotropins in hirsute women taking finasteride, and with the findings of other studies done on male patients(6,16).

Effects of finasteride on serum total testosterone levels in our study was a reduction at the third month of the study. Although remained in the normal range, the decrease was statistically significant ($p<0.05$). No changes or small increases within the normally accepted adult male ranges in testosterone levels were reported by some investigators in normal men wtih finasteride adminastration(6,16). In the previous studies, which were done in hirsute women with finasteride, statistically significant increases, but also within the normal female ranges, in total testosterone levels, were observed(5,10,23). Our result is conflicting with these results, but in a report of Ohtawa et al., although transient, reductions in testosterone levels were recorded during 5α-reductase inhibitor administration to male volunteers(12). In our opinion, in order to explain such discrepancies, more studies including large patient numbers must be done with the drug. On the other hand, finasteride did not affect the free testosterone levels of our patients.

Serum cortisol levels reduced at the first month of therapy in the present sdudy. The levels were within the normal range and returned to basal levels at the third monh. Fruzzetti et al. also reported a similar decline in their patient group(5). As the patients did not show either signs or symptoms of hypocortisolism, and values returned to pretreatment levels, this reduction is accepted to be unimportant. But taking together with the reduction of total testosterone levels, a suggestion of a transient reducing effect of the drug both on transcortine and sex hormone binding globulin concentrations can be made.

In conclusion, depending on the preliminary results of this study, finasteride seems to be a safe and effective drug for the treatment of hirsutism, but further investigations must be done to confirm this observation.

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EVALUATION OF PATIENTS WITH HASHIMOTO THYROIDITIS FOR THE RISK OF DEVELOPMENT OF THYROID LYMPHOMA: SIGNIFICANCE OF ULTRASONOGRAPHIC IMAGING AND FINE NEEDLE ASPIRATION BIOPSY*

Nilgün Başkal** • Sevim Güllü**** • Demet Çorapçıoğlu*** • Korgün Koral***** • A.Nuri Kamel** • Ali Rıza Uysal** • Gürbüz Erdoğan**

SUMMARY

The association of Hashimoto thyroiditis with malignant lymphoma of the thyroid is well known.An incidence of 27-100 % of Hashimoto thyroiditis in patients with thyroid lymphoma has been reported. Recently the detection of a pseudocystic pattern in the ultrasonographic examination of the thyroid was suggested as an indicator of thyroid lymphoma.Fine needle aspiration biopsy (FNAB) done in sites showing this pattern was also suggested in achieving diagnosis. From this point of view , in the present study , searching for a pseudocystic ultrasonographic pattern and performing FNAB from this site in patients with Hashimoto thyroiditis is recommended for the early diagnosis of thyroid lymphoma . Sixty patients with Hashimoto thyroiditis were evaluated. Thyroid ultrasonography was performed in all patients. In twelve (20 %) of the ultrasonographic examinations a pseudocystic pattern was detected but cytological examinations revealed no lymphoma. Still as the late diagnosis of thyroid lymphoma can mean a far more unfavorable outcome, we suggest that patients with Hashimoto thyroiditis should also be followed with ultrasonography and FNAB should be carried when such a suspected cystic lesion was detected.

Key Words: *Hashimoto thyroiditis, thyroid lymphoma,fine-needle aspiration biopsy, ultrasound diagnosis*

Hashimoto thyroiditis is a common chronic inflammatory disease of the thyroid gland.The histological findings could either be a diffuse lymphocytic infiltration and fibrosis or lymphocytes foci among thyroid follicles.Its association with malignant lymphoma of the thyroid is a well known feature of the disease (5-7,9,11). An increased risk of systemic proliferative and lymphoproliferative neoplasms(1.4 % vs expected 0.4 %) and also an increased risk of malignant thyroid lymphoma (0.5 % vs expected 0.007 %), in patients with Hashimoto thyroiditis were reported (8).An incidence of 27-100 % of Hashimoto thyroiditis in patients with thyroid lymphoma was also reported (3,6,13).

Ultrasonography and fine needle aspiration biopsy are the two diagnostic methods that have been applied to many thyroidal diseases, as well as Hashimoto thyroiditis (1,4,10, 12,14) .There are reports about the ultrasound pattern of the thyroid gland in Hashimoto thyroiditis. A diffuse low echogenicity as a consequence of lymphocytic infiltration was reported in Hashimoto thyroiditis patients. A very low echo amplitude or anechoic patterns were observed in patients who showed a greater lymphocytic infiltration in thyroidal biopsy specimens (10,14).

Recently, Matsuzuka et al reported an asymmetrical pseudocystic pattern with ultrasonography in 93% of patients with thyroid lymphoma,where as only 11% of patients with Hashimoto thyroiditis without thyroid lymphoma were found to be positive for this pattern (11). They also claimed that, fine needle aspiration biopsy (FNAB) from this site could make the diagnosis of thyroid lymphoma possible in 90% of the patients.

* This Study was reported as a poster in the 8th Balkan Congress of endocrinology.

** Professor, Endocrinology and Metabolic Diseases, Ankara University, Medical School.
*** Endocrinologyst Endocrinology and metabolic Diseases, Ankara University, Medical School.
**** Fellow, Endocrinology and Metabolic Diseases, Ankara University, Medical School.
***** Resident, Radiodiagnostic Department, Ankara University, Medical School.

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In the present study, we evaluated the patients with Hashimoto throiditis for such an ultrasonographic cystic pattern and a FNAB was performed whenever this pattern was detected. The aim was to develop a strategy for the early diagnosis of the thyroid lymphoma in patients with Hashimoto thyroiditis.

PATIENTS AND METHODS

Sixty patients with Hashimoto thyroiditis were included to the study.The diagnosis had been made on the basis of a firm, nodular thyroid enlargement, positive high antithyroidal antibody titers and FNAB of the gland. The patients were re-evaluated according to the study plan.Study group included 52 women and eight men of ages ranging from 18 to 66 years.

The duration of the goiters were between 2-25 years,as was learned from the histories of the patients.

Twelve patients were clinically hypothyroid, 14 patients had subclinical hypothyroidism, two had Hashitoxicosis and 32 were euthyroid at the time of the diagnosis.All were clinically and hormonally euthyroid when they were included to the study.

Free thyroxine and free triiodothyronine levels were measured by radioimmunoassay. Sensitive thyroid stimulating hormone, antimicrosomal antibody and antithroglobulin antibody titers were determined by immunoradiometric (IRMA) method .

An ultrasonographic examination of the thyroid gland was performed in each patient. Whenever an asymmetrical cystic pattern was observed, a FNAB from this site was done by the same radiologist, under ultrasonographic guidance.

Cytologic study of the obtained biopsy specimens were interpreted with a suspected diagnosis of thyroid lymphoma.

RESULTS

Sixty patients with a diagnosis of Hashimoto thyroiditis were evaluated. None of the patients had any new symptoms, such as rapid growing mass, hoarseness, dysphagia, all were asymptomatic.

With ultrasonography,12 of the 60 patients (20%) showed asymmetrical cystic patterns (Figure 1 shows the pseudocystic pattern). None of the specimens,obtained by FNAB from these cysts, showed any evidence of thyroid lymphoma.

DISCUSSION

The relationship between Hashimoto thyroiditis and thyroid lymphoma is a well known entity. Almost all of the reported thyroid lymphoma cases were found to be occur in patients with Hashimoto thyroiditis (3, 5-7,9,11,13). It was suggested that the chronic antigenic stimulation found in the chronic lymphocytic thyroiditis,was the cause of the thyroid lymphomas (2).

Fine-needle aspiration biopsy has been proposed for the diagnosis of the thyroidal diseases,as well as for the thyroid lymphoma (1,4). Thyroid

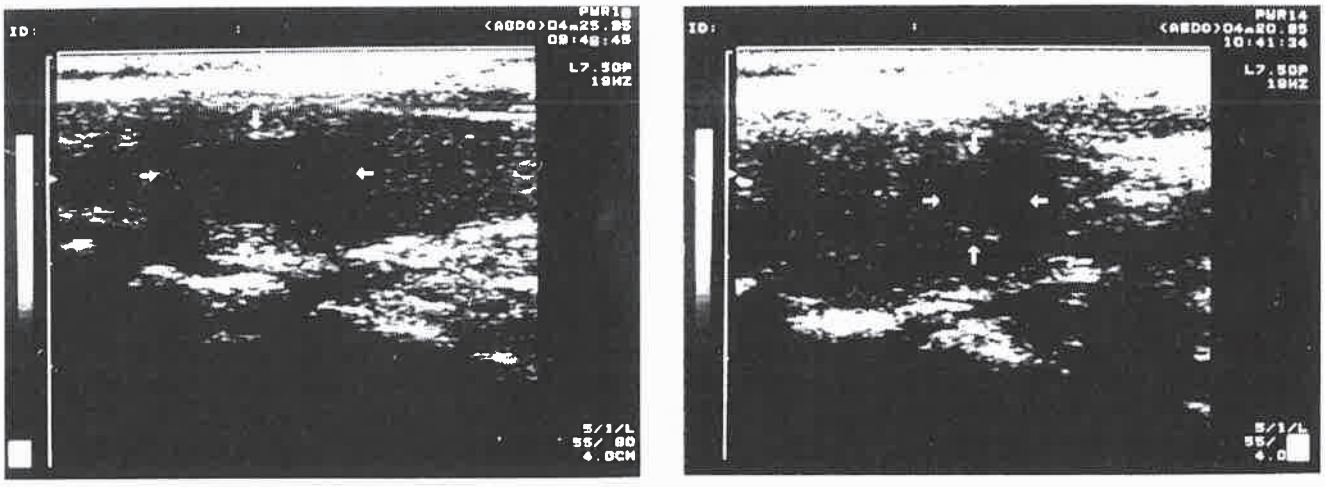

Figure 1: Pseudocystic Patterns detected in the patients with Hashimoto Thyroiditis Patients.

ultrasonography is also a noninvasive tool for the thyroid pathologies.The ultrasonographic examinations revealed hypoechoic or almost anechoic echogenicity patterns in the sites of the lymphocytic infiltration, in the patients with Hashimoto thyroiditis. The echo amplitude was found to be more decreased when the lymphocytic infiltration was high (9,10,12,14).

Infiltration of the thyroid gland with malignant lymphoid cells,either in a nodular or diffuse pattern,is the character of thyroid lymphomas. This involvement sites also shows lower echo amplitude as demonstrated by Matsuzuka et al (11).

Thyroid lymphoma has a fatal course ,but early diagnosis and initiating early treatment can improve prognosis. The patients with Hashimoto thyroiditis are at risk of developing thyroid lymphoma,as mentioned before.Therefore searching for a pseudocystic lesion with ultrasonography and performing a FNAB from this sites can make this early diagnosis possible in these patients. From this point of view we re-evaluated 60 patients with Hashimoto thyroiditis. Although we observed pseudocystic patterns in some of them, we could not able to demonstrate lymphoma cytologically.

In conclusion, as the primary malignant lymphoma of the thyroid occures more frequently in the patients with Hashimoto thyroiditis,we suggest to follow the patients with chronic lymphocytic thyroiditis with ultrasonography and FNAB.

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A NEW APPROACH TO SCHIZOPHRENIA PATHOGENESIS[1]

Ethem Akçıl[*] • Güzin Özelçi Kavas[*] • Engin Turan[**] • Coşkun Şarman[**]

SUMMARY

This work is done to investigate the role of reactive oxgen metabolites(ROM) in the pathogenesis of schizophrenia in wich organic pathologies have been suggested as playing an important role.

For this purpose, the red cell superoxide dismutase(SOD) activity and both the red cell and plasma copper and zinc concentrations were measured in 16 chronic schizophrenic patients. The results were compared statistically with the values of 15 healthy individuals.

There was an important increase in the red cell SOD activity and also in plasma copper concentrations of the schizophrenics while the red cell copper and zinc and plasma zinc concentrations were decreased, as compared to control values.

These data showed that SOD increases its activity in order to potentiate the antioxidant function against the increased production of ROM in schizophrenia. Copper and zinc alterations, as well as increase in SOD activity may play an important role in the pathogenesis of psychiatric cases.

Key Words: *Copper, schizophrenia, superoxide dismutase, zinc.*

The adaptation of the organism to environmental conditions requires behavioural, autonomic, endocrine and metabolic responses in order to preserve homeostasis The integration of these adaptive functions is assured by complex brain mechanisms. Any disorder in these complex brain mechanisms disturbs homeostasis.

Brain tissue is highly supplied by the oxygen. Aerobic metabolism in brain tissue increases with maturation and therefore increased levels of antioxidant defense is required(31). Brain tissue is predisposed to peroxidative damage due to its high metabolic rate and its high concentrations of polyunsaturated fatty acids which are highly susceptible to oxidation(7,23). Exposure of neurons to the reactive oxygen metabolites(ROM) as superoxide radical, hydrogen peroxide, hydroxyl radical and nitric oxide results in an imbalance in energy metabolism as well as the deleterious effects leading to cell death(12,18). The peroxidation of membrane lipids by a highly reactive free radical such as superoxide (O^-_2) anion has been reported to change the activities of membrane bound enzymes and receptors which could result in altered membrane permeability and neural transmission(17).

For the above reasons, the components of external and intracellular membrane need to be protected from oxidative damage for the normal functioning of a nerve cell. The antioxidant enzymes, superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), glutathione reductase (GR) and glucose-6-phosphate dehydrogenase(G6PDH) function in this way.

There are increasing number of reports about the organic lesions and the structural abnormalities of the schizophrenic brains in recent years(1,2,6,9,31). Various histopathological damages seen in schizophrenic brain tissues are of a

1 This work was presented at the International Trace Element Symposium on 9th-11th November 1993, Antalya, Turkey.

* Pathophysiology Department, Ankara University Faculty of Medicine, Assoc. Prof.
** Psychiatry Department, Ankara University Faculty of Medicine, Assoc. Prof.
*** Psychiatry Department, Ankara University Faculty of Medicine, Prof.

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developmental nature, and for this reason such a cerebral structure is vulnerable to acquired damage later in life(31).

Schizophrenia, which is a biochemically heterogeneous syndrome has been suggested as a disorder of both norepinephrine and dopamine systems and as a disorder in which there are increased production of ROM(4,10,13,16,32), damaging the cellular integrity, increasing blood-brain barrier permeability(12) leading to neurotoxic activity. The loss of brain tissue then causes some function in behavioural disturbances. The copper-zinc SOD, by increasing its activity is particularly important for the brain tissue in schizophrenic cases(1,2).

Considering these properties, we expected changes in the SOD activity and the concentrations of copper and zinc in schizophrenia. For this purpose, this preliminary assay is planned and initiated by the Department of Pathophysiology and the Department of Psychiatry of Ankara Medical School.

MATERIALS AND METHODS

Sixteen patients from both sexes who were 20-44 years old, whose diagnosis were schizophrenia being treated with neuroleptics were selected for the study. Fifteen healthy individuals in the same range of age were taken for the control group. The blood samples of both the controls and the patients were drawn in the morning always at the same time. The blood samples of totally 5-8 ml from fasting subjects were taken with polyethylene disposable syringes and stainless steel needles into two demineralized centrifuge tubes which contained heparin. Plasma and the red cell of each sample were separated by centrifugation and kept frozen at -20°C in polyethylene tubes until the determination of trace elements. The blood samples for Cu-Zn-SOD determination were studied immediately without keeping frozen.

Measurement of Trace Elements: The concentrations of trace elements were determined by Hitachi 180-70 model polarized Zeeman atomic absorption spectrophotometer(26,27).

The Red Cell Superoxide Dismutase Assay: The red cell SOD activity was determined according to Winterbourn's method by spectrophotometer(33).

After washing and hemolyzing the red cells, haemoglobin concentrations were adjusted to 10 gm per 100cc and by an extraction procedure the enzyme was obtained. For each sample to be assayed 6 tubes were set up containing different concentrations of the extract plus the given reactives. Three tubes containing no red cell extract were also included with each run. After an uniform illumunation optical densities were measured at 560 nm. Results were expressed as units of SOD per gram of haemoglobin and 1 unit was defined as the amount of enzyme causing half the maximum inhibition of NBT reduction. The results were compared with those of 15 healthy individuals.

Statistical analysis was carried out using Student's t test.

RESULTS

The results of this study are given in Table I. The red cell superoxide dismutase activities of schizophrenic patients were found to be increased significantly as compared to the controls. There were also remarkable changes in the red cell and plasma copper and zinc concentrations as shown in Table 1. Plasma copper concentrations were increased markedly in schizophrenic patients while decreased slightly in the red cell compared to the control group. Plasma zinc concentrations of the patients

Table I. The Red Cell Superoxide Dismutase (SOD) Activity and Plasma and The Red Cell Copper (Cu) and Zinc (Zn) Concentrations of Schizophrenic Patients.

Parameter	Controls (n = 15) X ± Sx	Schizophrenics (n = 16) X ± Sx	Statistical Analysis
The red cell SOD activity (U/g - Hb)	3096 ± 54	4448 ± 242	$p < 0.001$
Plasma Cu concentration (µg/dl)	72.53 ± 3.40	128.06 ± 6.10	$p < 0.001$
The red cell Cu concentration (µg/ml)	1.37 ± 0.80	1.14 ± 0.05	$p < 0.05$
Plasma Zn concentration (µg/dl)	113.40 ± 8.98	112.50 ± 4.33	$p > 0.05$
The red cell Zn concentration (µg/ml)	13.50 ± 0.58	6.91 ± 0.38	$p < 0.001$

did not show a remarkable alteration when compared to the controls. But there were significant decreases in the red cell zinc concentrations of schizophrenics compared to the controls.

DISCUSSION

Schizophrenia with its various structural, developmental and metabolic abnormalities (6, 22, 29, 30) is still an unsolved problem for researchers.

We have approached schizophrenia from another point of view. There exists a variety of biochemical mechanisms within the brain which result in the prduction of ROM. These include monoamine oxidase catalysed oxidation of catecholamine and dopamine, prostaglandin metabolism, Fenton iron-catalysis, activation of macrophage-type microglial cells, and nitric oxide generation by brain endothelia and neurones (10, 12, 13, 15, 16, 19, 28, 32). Increased production of ROM by the mechanisms above, initiates radical chain reactions resulting in the damage in the cellular integrity and increase in the blood-brain barrier permeability(19). The radical chain reactions include the proceeding the peroxidation of membranes, proteins and nucleic acids and ultimately lead to cell death(1).

Antioxidant enzymes scavenging ROM are capable or not in schizophrenic cases? It is reported in several papers that GPx activity is decreased but SOD activity is increased in schizophrenia(1,8,9). SOD is particularly important for the brain tissue since this enzyme contributes to the biosynthesis of neuromediator system(17,18), as well as the other vital functions. On the other hand because the other scavenger enzymes such as GPx and catalase activities are not effective as SOD in brain tissue so, the only intracellular effective antioxidant defense is provided by SOD(2,3,9). This enzyme is capable of compansating the excessive production of superoxide radicals by increasing its activity(1). In our study we also have found a marked increase in SOD activity by %60.7 showing correspondance with the literature data. Because our study was not done in autopsy material, we had to have measured the red cell SOD activity instead of neuronal SOD activity. We have seen that the effects of oxidative stress, which we have supposed to be an important factor in the pathogenesis of schizophrenia, have extended through the blood cells affecting their intracellular antioxidant status. Our results have supported the hypothesis proposed by some investigators; according to this hypothesis, following some environmental insu hich induces an increase in the rate of oxidative metabolism in the affected regions of the brain such as severe emotional stress, hyperoxia, exposure to a particular virus or toxin; there appears a vulnerability factor, increasing the risk of peroxidative damage to the critical brain structures such as limbic system(1,2,6,9,14,17,18,25).

Besides the above mechanism, it is reported that the alterations in the trace element concentrations might lead to psychiatric symptoms(24). Manser et al showed that serum zinc concentrations were decreased and copper concentrations were increased in neuropsychiatric patients(24). Indeed, we have shown that copper concentrations have altered both in plasma and in the red cell of schizophrenic patients. Copper ions are responsible for the activity of SOD(14). The increase we found in the plasma copper concentration may be the result of several factors. Among them, acute phase response is one of the most important factor. Several cytokines released during stressful events induce acute phase changes. Although the primary sources of these cytokines are blood monocytes, tissue macrophages, some specialized cells such as brain microglial and astroglial cells also produce these molecules. When produced, these cytokines induce the synthesis of acute phase proteins in liver resulting in an increase in blood copper concentrations(11). Another factor which may cause increase in plasma copper concentration is the increased rate of degradation of certain enzymes containing copper in their structures. The decreased MAO activity in schizophrenic cases seems to support this suggestion(5,20,21). The decreased red cell copper concentration in our study suggested that the utilization of this element have increased intracellularly for the reconstitution of SOD which have increased its activity. We have determined decreased zinc concentrations both in plasma and the red cells of schizophrenic patients as compared to the healthy individuals. This may also be related to the release of acute phase proteins as well as the increased zinc need intracellularly for the stability of SOD. While acute phase proteins lead to a decrease in blood and tissue zinc concentrations, the increased SOD activity contributes to this depletion by increasing the need for zinc. As a result, the decreased levels of zinc both in plasma and the red cells supports the possibility of increased utilization of zinc for adaptation to stress in schizophrenia.

In conclusion, schizophrenia is a syndrome containing visible and defined structural brain abnormalities which are possibly a developmental nature. Many factors may influence the pathophysiology of schizophrenia. By this preliminary assay, we present a new approach to the pathophysiology of the disease by ROM, the change in SOD activity and the alterations in trace element concentrations.

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EVALUATION OF PHADIATOP FOR THE SCREENING OF ATOPY IN ADULT TURKISH POPULATION: A COMPARATIVE STUDY

Betül Sin • Dilşad Mungan • Zeynep Mısırlıgil • Füsun Kalpaklıoğlu • Yavuz Demirel • Lütfü Gürbüz*

SUMMARY

History of atopy, skin tests, total IgE and Phadiatop were most commonly used for the screening of atopy. The aim of this study was to investigate the diagnostic value of Phadiatop test in allergy screening for adult Turkish population. In addition, Phadiatop results were compared with history of atopy, skin prick tests (SPTs), total and specific IgE levels. A total of 410 adults were included in the study. Based on history, clinical examination, SPTs, total and specific IgE, 216 subjects were found to be atopic, while 194 were nonatopic. Pharmacia CAP System (Kabi Pharmacia Diagnostics AB, Uppsala, Sweden) was used to measure Phadiatop, total and specific IgE levels. SPTs were performed with standard common inhalant allergens including grass, tree and weed pollens, moulds (Alternaria,Cladosporium, Aspergillus, Penicillium), Dermatophagoides pteronyssinus, Dermatophagoides farinae, cat and dog dander. There was a significant correlation between; positive Phadiatop test results and positive SPTs and also specific IgE ($p<0.001$). Phadiatop was found to have an 89.4 % sensitivity, 92.8 % specificity, 91 % efficiency, 93.2 % positive predictive value, an 88.7 % negative predictive value and these parameters for total IgE were 77.7%, 65.5%, 71.5%, 72.6%, 72% respectively. We conclude that Phadiatop may be considered as a first line in vitro screening test for atopy when compared to total IgE.

Key words: *Atopy, CAP-Phadiatop , screening.*

Prevalence rates of atopy and atopic diseases appear to have increased over the last few decades (1). To date, a number of diagnostic tests have been available for the assessment of allergy. Family and personal history of atopy, clinical data, skin tests, determination of total IgE were most commonly used for screening of atopy (2,3). Phadiatop, an in vitro diagnostic test for specific IgE to inhalant allergens was introduced in the clinical setting. A large number of studies on the clinical value of Phadiatop have been carried out by many investigators from different countries and Phadiatop was reported to be suitable as a first step investigation in suspected inhalant allergy. Phadiatop detects the presence of specific serum IgE against common inhalant allergens. But, the exact composition of the allergens coupled in the Phadiatop-CAP is not supplied by the manufacturer (4,5,6). However; test performance in screening for inhalant allergy may vary according to the geographical area of application, due to possible differences in the most relevant airborne allergens responsible for atopic diseases in a given country. The aim of this study was to assess the value of Phadiatop for diagnosing allergic diseases in our country and to find out to what extent the test can be used as a screening measure for atopy compared with; skin prick tests, total and specific IgE.

MATERIALS AND METHODS

Study population

A total of 410 individuals aged between 13 and 64 years were included in the study. Selection of the subjects were based on history of allergy and clinical data. Of the 410 subjects, 216 suffered from allergic rhinitis and/or asthma, while 194 individuals had no nasal or respiratory symptoms and history of atopy. Atopic subjects were selected among the outpatients referred to the Allergy Clinic and the nonatopics were healthy hospital staff members. A

* University of Ankara, Faculty of Medicine, Department of Allergic Diseases, Ankara-TURKEY

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standard diagnostic procedure was used , and it consisted of a medical history, physical examination , and skin prick tests. The medical history was based on responses to a self-administered questionnaire followed by an interview.

In vivo Tests

Skin Prick Tests (SPTs) were performed with standard common inhalant allergens including grass, tree and weed pollens, moulds (Alternaria,Cladosporium, Aspergillus, Penicillium), house dust mites (D.pteronyssinus, D.farinae), cat and dog dander (Stallergenés-Pastuer, France and ALK, Denmark). Histamine hydrochloride 10 mg/ml and 50% glycerol served as positive and negative controls, respectively. Test reactions were read after 20 minutes with recording of wheal diameters measured at right angles and interpreted in relation to the size of the positive control. A wheal at least 3mm larger than the negative control was considered as a positive response.

In vitro Tests

Pharmacia CAP system (Kabi Pharmacia Diagnostics AB, Uppsala, Sweden) was used to measure Phadiatop, total IgE and specific IgE concentrations in serum of all subjects. Sera from 410 subjects were analysed for total IgE, Phadiatop and specific IgE according to the manufacturer's instructions. The RAST-CAP panel comprises mixtures of grass pollen (gx1), tree pollen (tx7), weed pollen (wx1) and moulds (mx1) together with D. pteronyssinus (dx1), D. farinae (dx2), cat dander (ex1) and dog dander (ex5).

Specific IgE levels were expressed as either positive or negative for mixed groups of allergens (grass, tree, and weed pollens, moulds) and were considered to be positive if at least one RAST-CAP was class1 or higher for the other inhalant allergens (D. pteronyssinus, D. farinae, cat and dog dander). Serum total IgE values were expressed in kU/L and was considered to be positive at levels above >100 kU/L. Phadiatop test results were given either as negative (ratio≤1.00) or a positive outcome (ratio>1.00).

Final diagnosis: On the basis of positive history, confirmed by skin prick testing, the diagnosis of inhalant allergy was made. This final diagnosis was then compared to the results obtained with total IgE, specific IgE and Phadiatop tests. Standard methods were then used to calculate percentages of sensitivity, specificity, positive predictive value, negative predictive value and efficiency for both IgE and Phadiatop.

Statistics

Chi-square test and Fisher's exact test were used in analyses of the data. A p value of <0.05 was considered to be statistically significant.

RESULTS

We classified a subject as atopic if she or he had both allergic symptoms and positive SPTs to one or more inhalant allergens. Based on this criteria ; 216 subjects were diagnosed as atopics while 194 as nonatopics. Of the 194 nonatopic subjects, 90 male and 104 female, the mean age was 31.94±8.72 (ranged from 19 to 64). Atopic subjects were consisted of 88 male and 128 female, with a mean age

Table 1. Results of various diagnostic tests in atopic and nonatopic subjects

	Result	Phadiatop		RAST-CAP (Spe. IgE)		Total IgE*		Skin tests	
		No	%	No	%	No	%	No	%
Atopic	Positive	193	(89.4)	189	(87.5)	168	(77.8)	209	(96.8)
	Negative	23	(10.6)	27	(12.5)	48	(22.2)	7	(3.2)
	Total	216	100.0	216	100.0	216	100.0	216	100.0
Nonatopic	Positive	14	(7.2)	14	(7.2)	67	(34.5)	17	(8.8)
	Negative	180	(92.8)	180	(92.8)	127	(65.5)	177	(91.2)
	Total	194	100.0	194	100.0	194	100.0	194	100.1

* Positive : >100 kU/L
Negative: ≤100kU/L

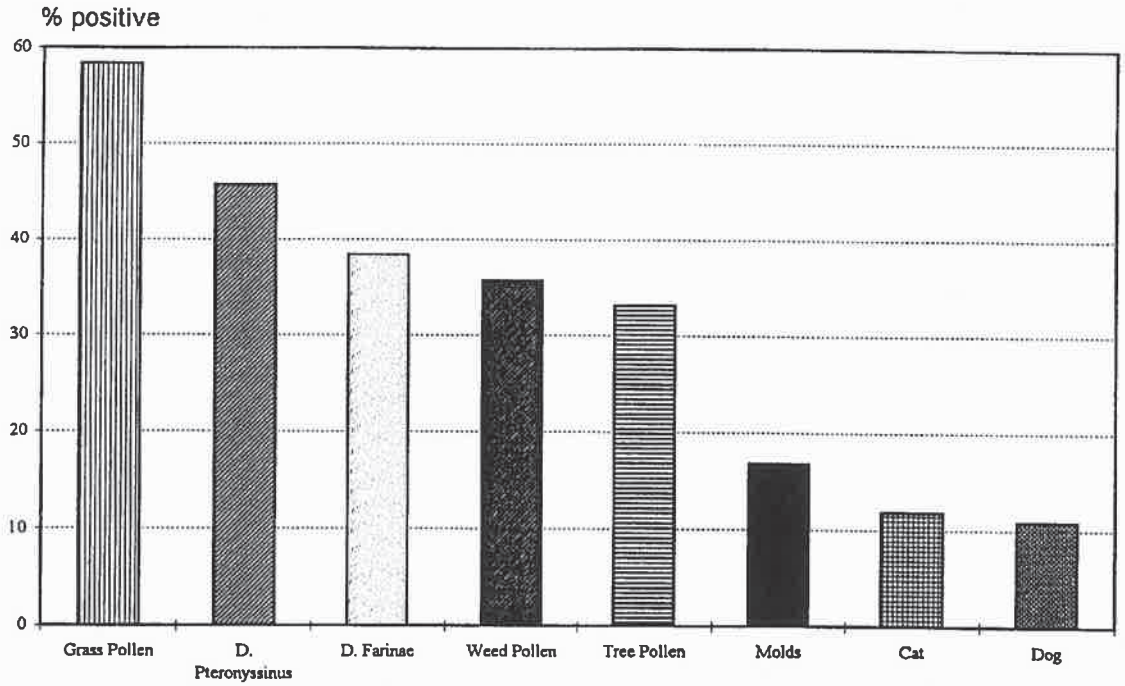

Fig. 1. Skin test sensitization rates for 8 inhalant allergens.

of 32.11±10.13 (range 18-63). We diagnosed allergic rhinitis in 43.9%, asthma in 8.1%, asthma and rhinitis in 43%, and the association of asthma ,rhinitis and urticaria in 5% of the atopic subjects.

The rates of skin test sensitivities of atopic subjects were shown in Figure 1. All of the 216 subjects with allergy symptoms and 17 out of 194 subjects without history of allergy and clinical symptoms had positive SPTs to one or more inhalant allergens. Of the 17 subjects in the nonatopic group with positive SPTs , 14 also had positive Phadiatop and specific IgE tests. Among the 216 atopic subjects, 193 were Phadiatop positive and 23 were negative. Of the 194 nonatopic subjects, 180 were Phadiatop negative and 14 were positive. Number of patients with positive and negative test results for Phadiatop, SPTs, total and specific IgE were shown in Table I for atopic and nonatopic subjects respectively. Phadiatop test had an 89.4% sensitivity, a 92.8% specificity, an 91% efficiency, a 93.2% positive predictive value and an 88.7% negative predictive value when compared with total IgE levels (Table II). Geometric mean of total IgE levels were; 218.16 kU/L and 49.43 kU/L in atopic and nonatopic cases, respectively.

There was a significant association between RAST-CAP and Phadiatop positivity rates for all allergens but especially higher in the grass pollen group (χ^2= 51.499, p<0.0001). In addition, the correlation between the degree of SPTs and Phadiatop positivity was highly significant (grass pollen χ^2 = 34.415 p<0.001, Der p χ^2 = 6.555 p<0.01, Der f χ^2 = 9.254 p<0.01). The relationship between positive SPTs and specific IgE results was also statistically significant (grass pollen χ^2 = 24.245 p<0.001, Der p χ^2 = 15.502 p<0.05, Der f χ^2 = 26.291 p<0.001). Phadiatop positivity was found to be correlated with higher IgE concentrations (χ^2 = 41.674, p<0.001) (Figure 2).

DISCUSSION

It is estimated that about 30% of the populations suffer from symptoms associated with atopic diseases (6,7). IgE tests have been powerful research tools for studying the mechanisms of atopic allergy (2,3). Because allergy is such a large clinical problem , routine IgE tests should become faster and simpler to perform whilst being more efficient and reliable in providing diagnosis.

To day, Phadiatop has been used as a routine tool in investigation of atopic diesases, and a large number of studies on the clinical utility of Phadiatop have been carried out (4,7,8). In this study; 193 out

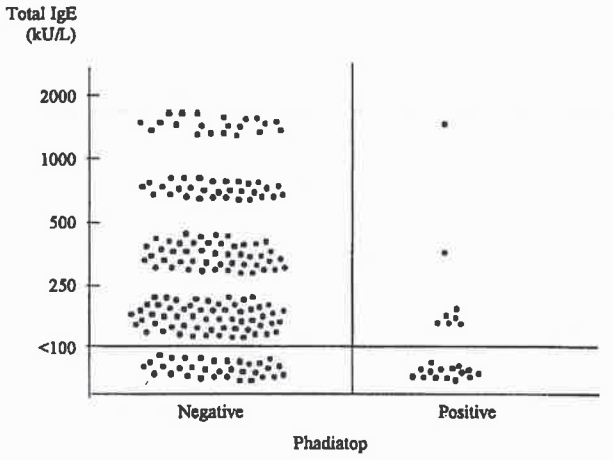

Fig. 2. Relationship between Phadiatop and total IgE among atopics.

Table 2. Screening of inhalant allergies in 410 adult subjects: comparison between Phadiatop and total IgE

Total IgE (Cut off > 100kU/)		Phadiatop
77.7	Sensitivity (%)	89.4
65.5	Specificity (%)	92.8
	Predictive value (%)	
71.5	Positive	93.2
72.6	Negative	88.7
72	Efficiency (%)	91

of the 216 allergic subjects were Phadiatop positive, however, of the 194 nonallergic subjects, 14 also had positive test results, thus placing Phadiatop's specificity at 92.8%, sensitivity at 89.4%, positive predictive value at 93.2% ,negative predictive value at 88.7% and efficiency at 91%. The diagnostic precision of CAP-Phadiatop found in our study seems to be in agreement with that found by other authors (8,9,10,11). The results of our study demonstrate that CAP-Phadiatop assay may provide a valuable, reliable and time saving method in screening atopic diseases. The correlations between RAST-CAP specific IgE antibodies for 8 inhalant allergens and Phadiatop as atopy screening test gave concordant results in our population. In addition, positive Phadiatop was well correlated with the degree of skin test positivity. Also, there was a significant association between positive SPTs and specific IgE, confirming previously published results (5,8,12,13). In this study; we investigated Phadiatop as supplied in Europe. From our results it is evident that Phadiatop is suitable for allergy screening also in our country.

Total IgE levels has been reported to be of insufficient sensitivity in several studies (5,14). In our study positive and negative predictive values of total IgE were 71.5% and 72.6 % respectively with a sensitivity of 77.7%, a specificity of 65.5% and an efficiency of 72%. When compared; Phadiatop positivity was found to be correlated with higher IgE concentrations. It is important to underline that total IgE levels can be increased also in nonallergic conditions; therefore high serum IgE levels may not lead to a correct diagnosis. However in some cases; clinical history may strongly indicate several sources of allergen not represented by Phadiatop which could be a food, venom, drug or an allergen only encountered in a factory, in such instances raised total IgE levels might be of value (6). It should be emphasized that Phadiatop is a useful assay especially in predicting inhalant allergy.

In clinical diagnostics, a patient history is the first step and should always be included in the diagnostic consideration. Interestingly, 17 out of 194 asymptomatic subjects had positive SPTs to one or more inhalant allergens in our study. 14 out of them also had both positive RAST-CAP and positive Phadiatop tests. These subjects had neither respiratory/nasal symptoms nor history of atopy. This was the reason for why we included these subjects in the nonatopic group. Prospective studies performed in the past have demonstrated that a remarkable number of asymptomatic subjects with positive skin tests develop respiratory allergic disease over the course of time (15). Therefore, SPT positivity in these cases without clinical symptomatology may be an indicator of latent allergy. In this respect; our 14 asymptomatic subjects with positive SPTs, positive specific IgE and positive Phadiatop test should have to be under observation, in order to monitor the possible appearence of future allergy symptoms.

We conclude that the diagnostic precision of Phadiatop found in this study is in agreement with that found by other authors. Results of our study indicates that Phadiatop has a higher diagnostic precision than total IgE in screening for inhalant allergy. It is important to underline that a complete diagnostic procedure; correlating history of atopy, skin tests and/or in vitro identification of specific IgE is mandatory in screening inhalant allergy and can not be replaced by a single assay. The use of Phadiatop

allows this; long, expensive and time consuming procedure to be restricted to the Phadiatop positive population only. Finally, CAP-Phadiatop seems to be suitable as a first step investigation in suspected inhalant allergy diagnosing in our country.

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EVALUATION OF THE HYPOTHALAMOPITUITARY-GONADAL AXIS IN THE NEONATAL, PREPUBERTAL, AND PUBERTAL CRYPTHORCHIDIC PATIENTS

Merih Berberoğlu* • Gönül Öcal** • Sema Akçurin*** • Nihal Memioğlu***

SUMMARY

Objective:

Normal functional capacity of hypothalamo-pituitary-gonadal (HPG) axis plays a vital part in the descent of the testis. The aim of the study was asses the function of HPG axis in cryptorchidic and normal healty children at different age groups (neonatal, infancy, prepubertal and pubertal).

Study design:

Functional tests which include determination of basal and stimulated testosterone (with hCG), basal and stimulated (with GnRH) LH-FSH, and night time profile of gonadotropins during the first 4 hours of sleep were done.

Hypothalamic-pituitary-gonad axis was evaluated in total of 38 cryptorchidic patients in 4 different age groups of which, 9 were neonates, 10 were infants (mean age; 1.22±0.63 years), 10 were prepubertal (mean age 6.3±2,3 years) and 9 were pubertal (mean age, 13±1.3 years). Evaluation was also carried out in total of 38 healthy children of which 10 were neonates, 10 were infants (mean age, 0,6±0,4 years), 10 were prepubertal (mean ages 8.8±2.3 years) and 8 were pubertal (mean age 14,3±0.7 years).

Results:

Neonatal cryptorchidic cases showed sufficient postnatal testesteron increase but insufficient LH elevation compared with the controls.

Leydig dysfunction was determined in 40% of cryptorchidic infants. In these cases the most important finding was the high compensatory basal and stimulated (according to control response) FSH levels.

In the prepubertal cryptorchidic patients, progress of Leydig reserve decrease (60% leyding duysfunction) and continuation of compensatory FSH increase were observed.

In the pubertal patients, basal and stimulated testosterone values were found considerably insufficient when compared with the control group. Inspite of 89% progression of leyding dysfunction, insufficient hypothalamic-pituitary compensation response was observed.

Conclusion:

Gonadal dysfunction begins in infancy and progressive damage occurs in prepuberty and puberty in cryptorchidic patients.

Keyword: *Crypthorchidism*

Cryptorchidim is one of the most common congenital anomalies in childhood. Various etiological hypotheses (mechanical factors, intrinsic abnormalities of the testes, disturbances in the hypothalamopituitary axis) have been formulated. Defects in the HPG axis or a structural abnormality may result in cryptorchidism. Indeed there are a variety of syndromes characterised by defects in gonadotropin production, androgen syntheses or androgen action in which cryptorchidism is common. One example of this is Kallman's syndrome. In these cases this condition causes varying degrees of deficient virilization(3). Nevertheless in the isolated cases, cryptorchidism probably results from temporary incomplete involvement of the HPG axis (16). It's difficult to evaluate HPG functions at all age groups. It needs several complicated hormonal tests. Therefore, there is limited data in the literature. The aim of this study was to evaluate HPG axis in cryptorchidic patients at different age groups, to compare the results with the according control groups and to try to elucidate these questions:

* Assistant Professor
** Professor
*** Resident in Pediatric Endocrinology

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1. Is there any subclinical or overt hormonal events which reflect HPG dysfunction in the neonatal cryptorchidic patients?

2. What is the effect of cryptorchidism on the testes functions in the consecutive years? Are there any warning sings?

3. What is the response of HPG axis to gonadal dysfunction at different age groups when it is present?

MATERIAL AND METHODS

The study has been done in total of 38 cryptorchidic patients at four different age groups, of which 9 were neonates, 10 were infants, 10 were prepubertal and 9 were pubertal. In all of the patients height, weight, stretch penile length, penile circumference, testes localization and testes volume were evaluated. Penile measurements were interpreted by the Lee criteria in neonates and infants (12). In prepubertal and pubertal stages Turkish Children standars were used for interpretation (10). Testes volume was measured by Prader orchidometer and Tanner Marshall classification has been used for pubertal staging (17,22).

Laboratory Assessment of HPG Axis:

** Baseline serum LH, FSH, testosterone, determinations.*

** Human chorionic gonadotrophin Test:* Testing of hCG stimulation was done with a dose of 2000 IU/m² for 5 days intramuscularly to asses Leydig cell function. The samples for testosterone were taken basally and 24 hours after the last hCG injection. This test was performed in all of the cryptorchidic patients except for neonates and the control groups. The responses above 2 ng/ml and 6-8 ng/ml for prepubertal and pubertal events respectively were accepted as normal leydig function(19,23).

** LHRH stimulation test:* This test gives information about the amount of both gonadotropins. LHRH was injected intravenously as a bolus of 100 microgram and blood samples for LH and FSH were collected before injection and then at 40-60-120 minutes (19). This test was done in all of the cryptrochidic patients except for neonates and the infantile control subjects. The results were compared with the control groups. The responses above +2SD were considered exaggerated and below -2SD were considered insufficient.

**Nocturnal physiological gonodotropin secretion:* Prepubertal and pubertal crypthorchidic patients and control cases underwent investigation of gonadotropin secretion during the first four hours of nocturnal sleep. Blood samples for LH, FSH were taken at 30 min. intervals (4). LH, FSH serum concentrations were assessed with Amerlex-M radioimmunassay kits. Testosterone was assessed with Coat-A-Count total testosterone kit.

Statistical Method:

Differences between the groups were analyzed by student's t test. P levels <0.05 were considered significant.

Subjects:

Neonatal Patients: All 9 crypthorchidic newborn's were older then 37 weeks and all were appropriate for gestational age. Their penile lengths were in the normal range. The blood samples were withdrawn after the postnatal first week early in the morning. The results were compared with the control neonates (n: 10) which were at the same gestational age and birth weight.

Infancy patients: Ten cryptorchidic infants aged between 0.4-2,1 years (mean age 1.22±0,63) were evaluated for HPG axis and compared with the ten healty infants aged between 0,2-1.5 years (mean age 0,6.04±0,4) Three of the cryptorchidics also had micropenis. Nocturnal gonadotropin secretion samplings weren't performed in this group for its difficulty. However diurnal LH and FSH serum samples were taken to demonstrate probable episodic release of gonadotropins(3). In addition, stimulation wasn't done in control healty infantile boys.

Prepubertal boys: Ten prepubertal cryptorchidic boys aged between 3.5-10 years (mean age 6.3±2.3 years) were evaluated. Three of them had micropenis, one of them had hypospadias. The patients were compared with 10 healthy boys aged between 5-11.3 years (mean age 8.8±2.3 years). All of them were at Tanner 1 pubertal stage. Human chorionic gonadotrophin stimulation test wasn't permitted in the control group.

Pubertal boys: Nine cryptorchidic pubertal patients aged between 10.8-15 years (mean age) 13.1±1.3 years) who were admitted to the outpatient clinics were included in the study. Three of them had also micropenis. Pubertal stages of all of them were over Tanner 1. All the laboratory tests evaluating HPG axis were performed in the patients. Eight normal subjects of comparable pubertal stage

Table I: Anthropometric and hormonal features of normal and crypthorchidic neonates.

	BW gr.	BH cm.	LH mIU/ml	FSH mIU/ml	Testosterone ng/ml
Control n=10	3330±309	49.9±1.3	21.2±11.2	3.05±2	2.87±3
Patients	3061±492	48.5±2.7	14.8±5.1	3.05±3	2.33±2
	Significance		p<0.05	p>0.05	p>0.05

BW: Birth weight, BH: Birth height

aged between 13-15.5 years (mean age 14.3±0.78 years) served as controls. Human chorionic gonadotrophin stimulation test couldn't be performed in pubertal controls like other control subjects for same reason.

RESULTS

In 76% of the cases cryptorchidism was bilateral. It was unilateral in the remaining 24%. The right side was more often affected (77%) than the left (23%). Of the 38 boys 21% had micropenis, 5.2%had hypospadias and 2.6%had inguinal hernia.

Neonatal patients: The results of neonatal cryptorchidic patients and control subjects are given in table I. Basal LH levels were significantly lower than those in normal subjects -p<0.05-, furthermore postnatal testosterone increase was sufficient.

Infantile patients: Comparison of the controls and cryptorchidic infants is given in table 2. Basal FSH levels were significantly higher than controls (p<0.05). In these cases leydig dysfunction was observed in 40%. The effect of LHRH on mean serum LH, FSH concentrations are also shown in table 2.

Prepubertal patients: Table 3 shows comparison of the prepubertal patients with the control cases. Means serum basal LH, FSH testosterone levels were not statistically different from those in normal subjects (p>0,05).

Mean stimulated testosterone with hCG was in the normal range (2.54±2.9 ng/ml). Nevertheless 60% of patients showed leydig dysfunction. A total of 50% of patients showed exaggerated, 20% showed normal and 30% showed insufficient LH response and 30% of patinets showed exaggerated, 60% showed normal and 10% showed insufficient FSH response to GnRH. In the nocturnal gonadotrophin secretion evaluation, FSH levels were significantly higher than the controls (p <0.05).

Pubertal patients: Table 4 shows comparison of the pubertal patents with the control cases. Mean stimulated testosterone value was lower then the reference value. Eighty eight point eight percent of patients showed leydig dysfunction. A total of 11,1% patients showed exaggerated, 55.6% showed normal and 33.3% showed insufficient LH response and 22.1% showed exaggerated, 44.6% showed normal and 33.3% showed insufficient FSH response to GnRH. Nocturnal gonadotrophin secretion profiles weren't statistically different from those of the control cases (p>0.05). Changing basal LH, FSH testosterone and stimulated testosterone values according to different age groups are given in Figure 1 and 2 respectively. Changing pituitary response according to leydig dysfunction in prepubertal and pubertal crypthorchidic patients are shown in Figure 3.

DISCUSSION

Aethiology of cryptorchidism in many patients is at the hypophyseal/hyothalamic level and

Table 2: Hormonal values of normal and crypthorchidic infants

				BASAL		Stimulated With LHRH	
	AGE (Year)	Basal Testesterone	Stimulated Testesterone	LH mIU/ml	FSH mIU/ml	LH Peak mIU/ml	FSH Peak mIU/ml
Control n=10	0.604±0.4	0.365±0.7	2-3*	1.39±0.9	0.85±0.4	-	-
Patients n=10	1.22±0.6	0.29±0.5	2.7±1.9	2.92±2.4	1.63±1.4	12.4±9.2	8.3±5.6
Significance:		p>0.05		p>0.05	p<0.01		

* = Reference value

Table 3: Hormonal features of normal and crypthorchidic prepubertal children

				BASAL		Stimulated with LHRH		Nocturnal	
	AGE (Year)	Basal Testesterone	Stimulated Testesterone	LH mIU/ml	FSH mIU/ml	LH Peak mIU/ml	FSH Peak mIU/ml	LH Peak mIU/ml	FSH Peak mIU/m
Control n=10	8.85±2.3	0.10±0.06	2-3*	2.25±0.6	1.6±1	10.9±2.5	7.32±3.4	4.34±1.8	3.96±2.1
Patients n=10	6.36±2.3	0.32±0.4	2.5±2.9	2.9±2.4	2.3±1.2	7±3	7.4±3.7	4.78±2.7	4.85±4.2
Significance:		p>0.05		p>0.05	p>0.05	p>0.05	p>0.05	p>0.05	p<0.05

*= Reference value

Table 4: Hormonal features of normal and crypthorchidic pubertel subjects

				BASAL		Stimulated with LHRH		Nocturnal	
	AGE (Year)	Basal Testesterone	Stimulated Testesterone	LH mIU/ml	FSH mIU/ml	LH Peak mIU/ml	FSH Peak mIU/ml	LH Peak mIU/ml	FSH Peak mIU/m
Control n=9	14.35±0.78	1.63±0.7	6-8*	4.5±2.9	3.9±2.8	32.3±12.6	10.46±4.78	9.6±2.4	6.9±2.8
Patients n=8	13.16±1.3	0.3±0.3	1.77±1.9	2.35±1.8	2.14±1.8	18.1±13.17	6.7±3.2	5.17±2.2	3.97±15
Significance:		p<0.05		p>0.05	p>0.05	p<0.05	p>0.05	p>0.05	p>0.05

*= Reference value

involves abnormalities of LH/FSH secretion, with the resulting testicular pathology being secondary to impaired gonadotropin secretion (5,13,20). Cryptorchidism can be consisted as overt or latent incomplete form of hypotalamo-pituiter dysfunction (13). In this study to evaluate HPG axis in cryptorchidic patients at the different ages and to compare the results with the controls confirmed very important findings. Control results had been elucidated for the interpretation of cryptorchidics results.

Neonates: Human studies noted a decrease in LH secretion reserve in cryprochidic neonates which continued throughout childhood (16,5,2,8,7). They also noted lower testosterone levels. It is apparent that the postnatal impaired gonadotropin release in episodic pulses is the most important factor to handicap descending testes.

Gendral found that testosterone levels at 1-3 months in cryptorchidic infants were lower than the control group (7). Low postnatal testosterone levels were more significant in preterms which have immature HPG axis. In our study all neonatal cryptorchidic events showed postnatal elevated LH, FSH and increased testosterone levels except one patient. However LH levels were lower than the normal subjects. Sufficient postnatal testosterone increase in neonatal cryptorchidics suggests that leydig functions are normal in the neonatal period. Low LH increases according to controls can be explained as an incomplete form of hypotalamo-pituitary dysfunction in the fetal period. The six cryptorchidic neonates were followed up longitudinally. Five of them showed spontaneous descending in the first 6 month of life. One of the neonate, had low postnatal testosterone level and his testes did not descent. Evaluation of the postnatal testosterone and gonadotropin levels in cryplorchidic neonates can provide useful information about spontaneous descending of the testicles. On the other hand this suggestion needs more investigation.

Infancy: All of the evaluated cryptorchidic infants were older than 6 months. This is the time when most of the cases demontstrate spontaneous descending. In the cryptorchidic infants the most

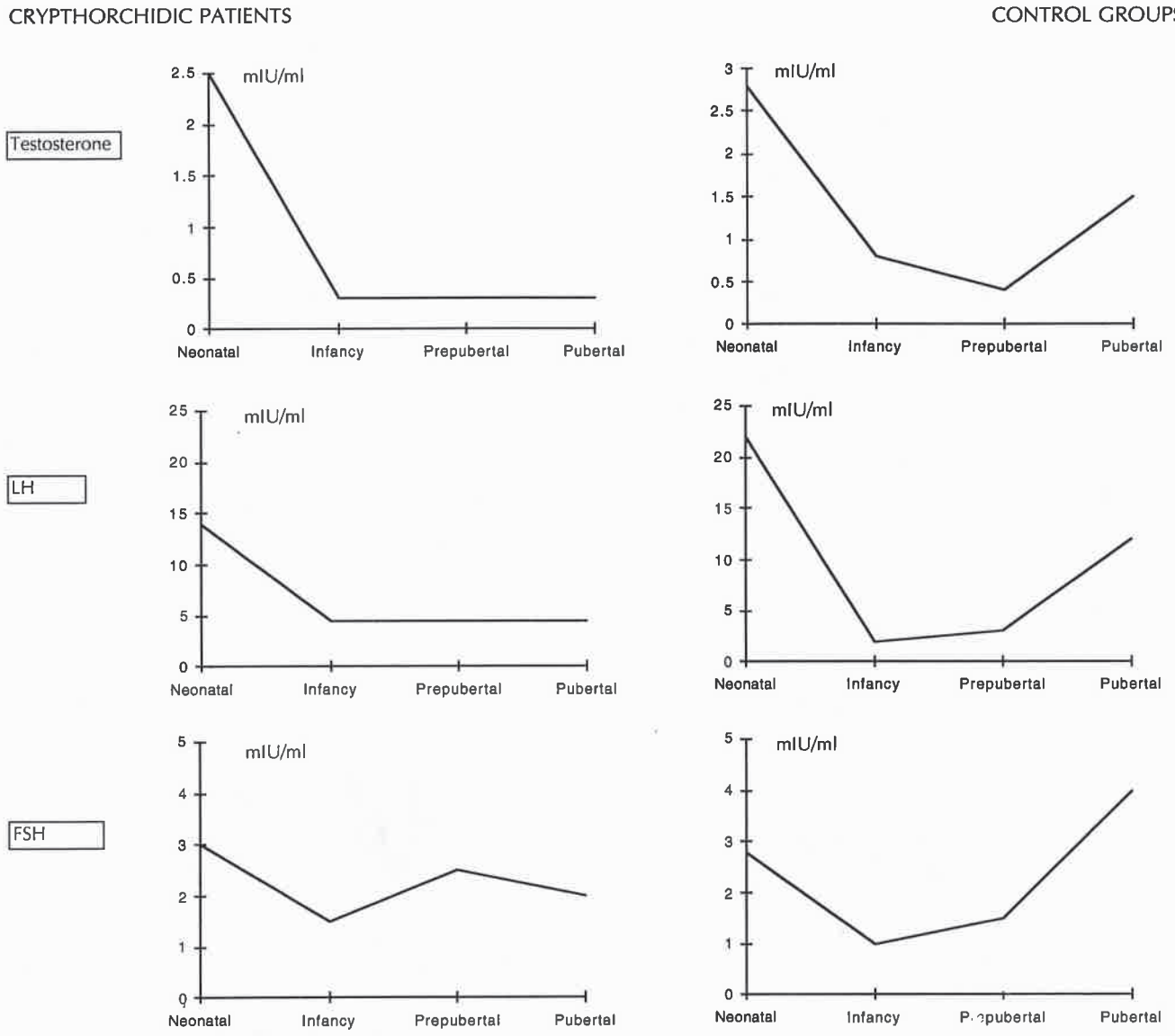

Figure 1: Differences of basal LH, FSH, testosterone values according to childhood stage

important finding was the high compensatory FSH level. This observation has also been reported by Sirvent (21). A experimental study also noted the enhanced FSH in the cryptorchidic rats (16). Histologic studies showed that the first finding of testicular damage was progressive loss in the size of the seminiferous tubule (5). The elevated FSH would be an expression of tubular damage and indeed it was higher when the tubule was more disrupted (11). According to some authors, elevated FSH levels indicate a defect in inhibin secretion (19). If it is true we should observe elevated FSH levels in neonatal cryptorchidics also.

Leydig cell stimulation using hCG is particularly helpful in children with cryptorchidism to identify leydig disfunction. In published reports, variability in the response the hCG in cryptorchidic children have been reported (1,6,14,15). Garg and coworkers had a good response to hCG in cryptorchidic boys (6). This is in contrast with other studies where testosterone is found be low (1,14,15). In our study 4 infants (40%) showed inadequate response which predicted leydig dysfunction. However mean stimulated testosterone value was in the normal range.

Prepubertal: There are published reports which notify both normal and abnormal HPG function in

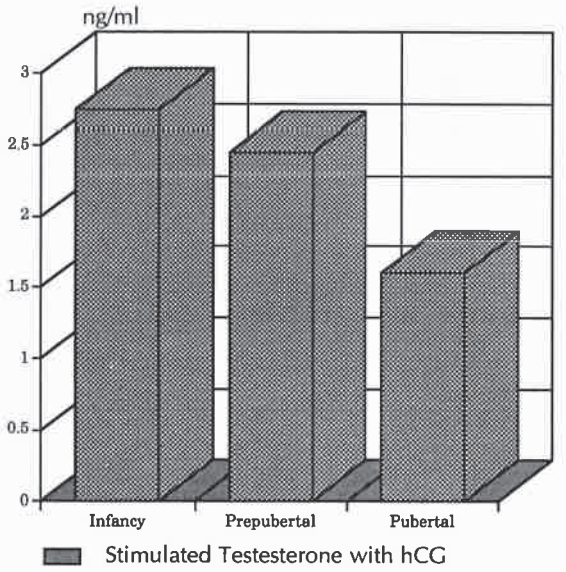

Figure 2: Stimulated testosterone responses according to age in crypthorchidic patients

cryptorchidic prepubertal patients (5,13,14). Martinetti and co-workers found no difference between patients and controls in LH and FSH after GnRH stimulation (14). High compensatory basal FSH level which have been found in infancy were not observed in our prepubertal cryptorchidics. However this finding was observed in nocturnal gonadotrophin secretion. Nocturnal peak FSH was significantly higher than the control group. This observation is in agreement with Sirvent et al (21). In the present study we demonstrate exaggerated and insufficient either LH or FSH response to LHRH stimulation. But definite conclusion is not easy owing to the small number of subjects in the trial. In our prepubertal crytorchidics progress of leydig dysfunction was also found. Six children (60%) had inadequate testosterone response to hCG. This is similar to that reported by Anoussakis et al (1). However this is in contrast with Garg's study (6).

Pubertal: Findings of the pubertal cryptorchidics

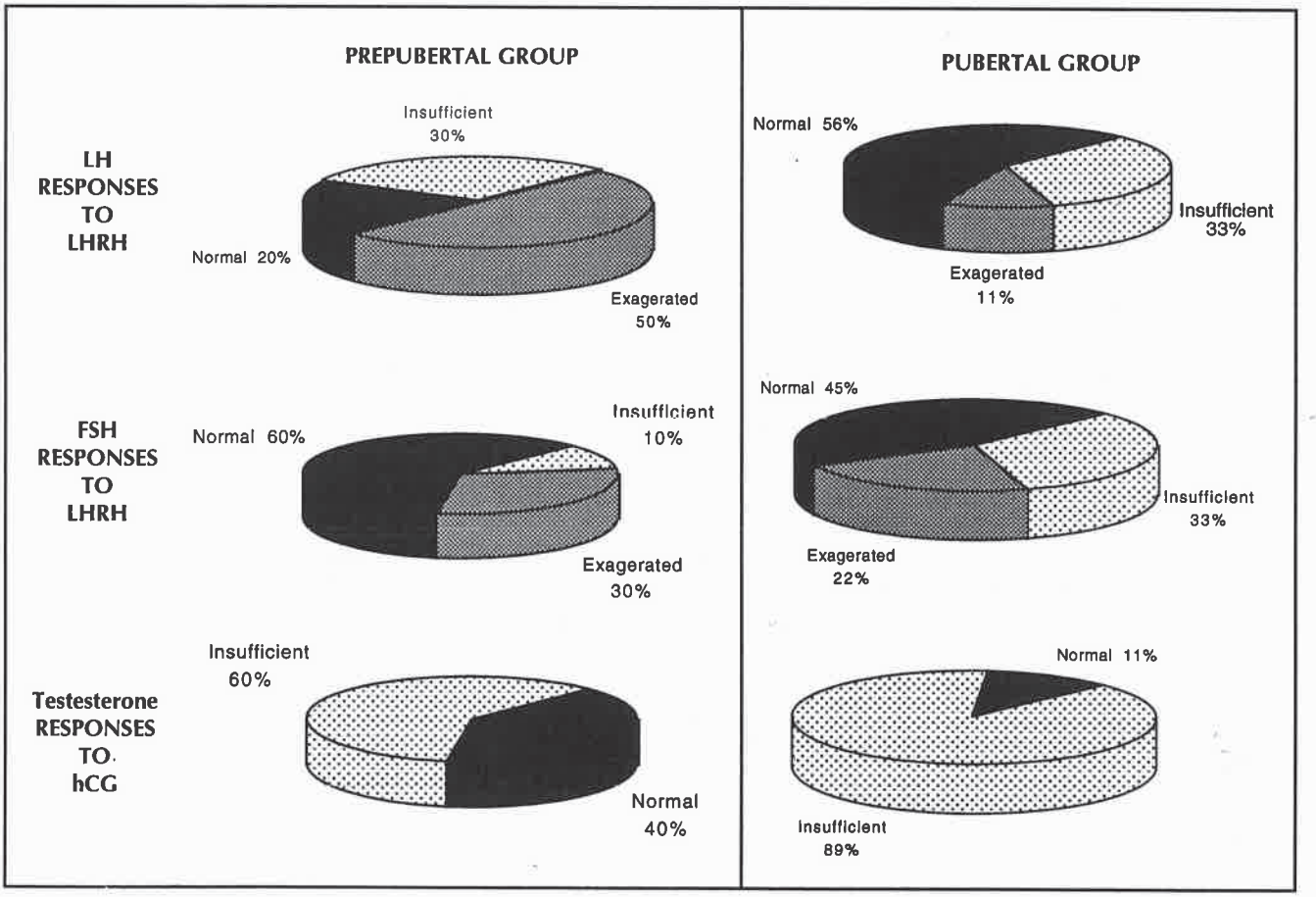

Figure 3: Gonadotrophin response distribution according to Leydig cell functions in prepubertal and pubertal crypthorchidisc

which indicated important problems pointed to HPG dysfunction. Basal and stimulated testosterone with hCG were significantly lower than the control group. Especially low stimulated testosterone levels suggested that the leydig functions were clearly disrupted (89%). In spite of leydig dysfunction, we have not observed compensatory high gonadotrophin response in pubertal cryptorchidics. Furthermore gonadotrophin response to LHRH was blunted. This finding suggests that the HPG axis is insufficient in pubertal stage.

How puberty can occur with this leydig dysfunction, is a question to be answered. Normal secondary sexual characteristics and puberty can occur even when testosterone levels are 1/16th of normal (13,18). Incomplete form of hypogonadism can be masked.

One of the primary sequelae of cryptorchidism is infertility. It is reported that 10% of infertile subjetcs are affected or had been affected by cryptorchidism (9). Seventy eight percent of cryptorchidic patients who were subjected to postpubertal orchidopexy and who had normally sized testes showed various degrees of oligospermia in Grasso's series (9). This study is in agreement with our observation of leydig dysfunction.

CONCLUSION

Because there exists an incomplete or complete insufficiency in HPG axis in the cryptorchidic cases, hormonal studies should be done in all, including the cryptorchidic newborns.

Gonadal dysfunction begins in infancy and irreversible damage occurs in prepuberty and puberty. Appropriate treatment should be planned soon after the first year of life, when spontaneous descending may occur.

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RESECTION OF VENA CAVAL THROMBI EXTENDING TO RIGHT ATRIUM CAUSED BY RENAL CELL CARCINOMA VIA CARDIOPULMONARY BYPASS AND DEEP HYPOTHERMIC CIRCULATORY ARREST

Ümit Özyurda* • Haldun Özberrak** • Atilla Aral*** • Hakkı Akalın****

SUMMARY

Renal Carcinoma with direct extension into the vena cava occurs in approximately 4% of all patients with this neoplasm. Presently, surgical extirpation is the only form of therapy that can result in cure. Recently management of extensive vena caval involvement has involved the use of cardiopulmonary bypass with deep hypothermic circulatory arrest.

In this report, we described management of renal carcinoma with vena caval thombi, via cardiopulmonary bypass and deep hypothermic circulatory arrest.

Key Words: *Carcinoma, vena caval thrombus, cardiopulmonary bypass, hypothermia*

Renal cell carcinoma with direct extension into the vena cava occurs in approximately 4% of all patients with this type of neoplasm (2,9). Extension of the renal cell tumor thrombus within the vena cava can be categorized as being located below the insertion of the hepatic veins (type I), above the insertion of hepatic veins but not intra-atrial involvement (type II) and intra-atrial involvement (type III). Resection of renal thrombus with infrahepatic vena cava extension (type I) usually can be performed by standard surgical techniques (2). However, types II and III tumors require a more complex surgical approach. Several methods have been described to remove these tumors (3,10) of which cardiopulmonary bypass with hypothermia and temporary circulatory arrest has been the most enthusiastic method recently (4,7).

CASE REPORT

A 58 year old man presented with the onset of gross hematuria and disuria has ben consulted in Urology department. The examination revealed right renal tumor and thrombi in the vena cava inferior.

Ultrasonography exhibited spherical, hypoechoic and anechoic smooth 7x7 tumoral mass at night kidney, located at the middle right of the vena hepatica that cause distorsion of the vena porta (Fig. I). Doppler ultrasonography revealed large vena caval thrombus. Computed tomography was judged to show a lobulated solid mass with necrotic spaces deforming the collecting system at right kidney. Thrombus extending between the bifurcation of the iliac veins and right atrium was detected (Fig. II). Magnetic resonans imaging revealed a wide heterogen solid mass located at the lower half of right kidney with tumor thrombus located in the right vena renalis and vena cava inferior extending to the right atrium (Fig. III). No metastatic disease was identified by bone scan, chest tomography or magnetic resonans imaging of the head and the abdomen.

* Associate Professor of Cardiiovascular Surgery of Ankara University Faculty of Medicine
** Resident of Cardiovascular Surgery of Ankara University Faculty of Medicine
*** Cardiovascular Surgeon of Cardiovascular Surgery of Ankara University Faculty of Medicine
**** Professor of Cardiovascular Surgery of Ankara University Faculty of Medicine

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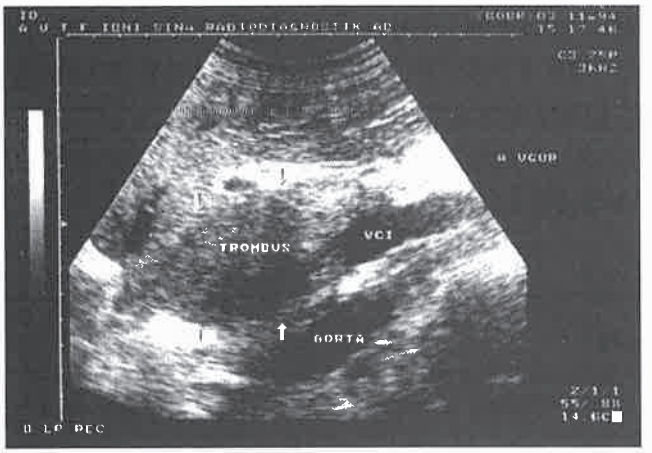

Figure I.

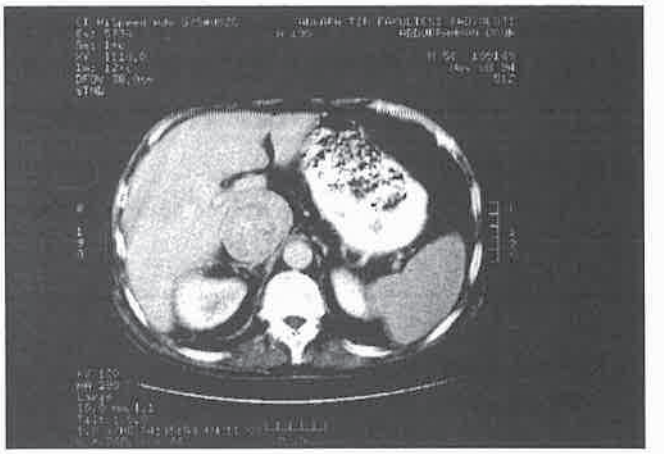

Figure II.

MANAGEMENT

At surgery; intra-arterial and Swan-Ganz catheters were placed. Following radical nephrectomy median sternotomy was performed. Pericardial patch was resected for use in case of inferior caval plasty. Aorta and right atrium was cannulated. Cardiopulmonary bypass initiated, and the body temperature was slowly lowered. Aorta was cross clamped and cardioplegic solution was administered through aortic root canula. Cooling was facilitated by iced saline lavage of the pericardial cavity. Cardiopulmonary bypass was terminated as the core temperature of 20° C has been achieved and the blood volume was drained into the pump. At this temperature approximately sixty minutes of safe cold ischemia time is possible to complete the operation.

A vertical incision was made in the anterolateral aspect of the vena cava over the thrombus extending several centimeters superiorly above the renal vein. The inferior aspect of the incision was curved laterally, and posteriorly in order to completely circumscribe the ostium of the renal vein. Thrombus was gently teased with forceps from the vena cava and also right atriotomy was made and thrombus was removed by digital extraction. Tumor invasion to VCI wall at the level of right renal vein was resected and reconstructed primarily. After removal of the thrombus, the interior of the vena cava was viewed and palpated from the renal vein to the right atrium and complete removal of the thrombi was justified. Vena cava was closed primarily by (4/0) monofilament polypropylen running sutures, cardiopulmonary bypass was initiated. By the end of the rewarming phase two liters of "Hot Shot" warm blood cardioplegia was administered and heart started to beat spontaneously. No inotropic support was needed. Circulatory arrest time was forty-nine minutes. The pathological investigation of the tumor revealed renal cell carcinoma. The patient had no problem in the postoperative course and discharged from the hospital in a week. Six months later, control CT revealed patent vena cava inferior (Fig. IV).

DISCUSSION

Renal carcinoma with vena caval involvement without lymphatic spread or distant metastases should be managed by aggressive surgical extirpation. If the lesion is untreated the natural history is one of the sudden death or carcinomatosis within 12 months (5). There is no definitive radiation therapy, chemotherapy or immunotherapy available but recent reports of survival following complete resection of the tumor has been encouraging (4,10). Autopsy reports have revealed that, the tumor can involve the kidney and the vena cava alone, without metastatic disease, which is consistent with reports of surgical care (1). The surgical approach to achieve complete excision of the tumor and removal of the thrombus without distal embolization depends on the level of the thrombus within the cava. There is a general agreement that type I tumors are best managed by standart radical

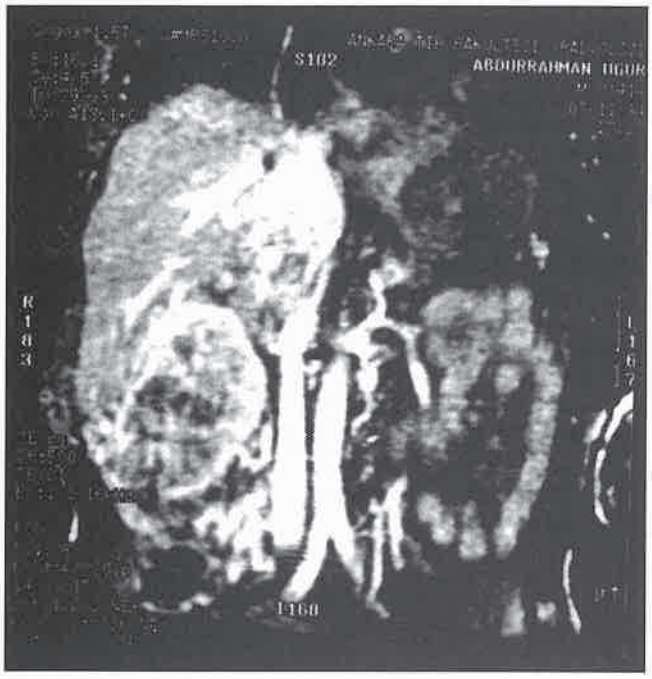

Figure III.

nephrectomy. The thrombus is removed by obtaining control of the vena cava proximally and distally without the necessity of cardiopulmonary bypass or lower torso circulatory arrest (2). There is also agreement that type III tumors require cardiopulmonary bypass with temporary hypothermic arrest for safe and effective removal (4,7,10). However there is no agreement in the literature as to the best management of type II tumors. A review of the literature revealed several techniques, each with its specific advantages and selective morbidity. Pritchett et. al. advocate mobilization of the liver and the vena cava via thoracoabdominal incision (8). Although this technique requires hepatic, bowel and right renal ischemia, and resulted in an average blood loss of 5466 cc., there were no intraoperative death and no heparinization was required. However, postoperative complications did include hepatic dysfunction and renal failure requiring dialysis. Management of hypotension resulting from obtaining vascular control using a "Rummel tourniquet" on the supradiaphragmatic inferior vena cava

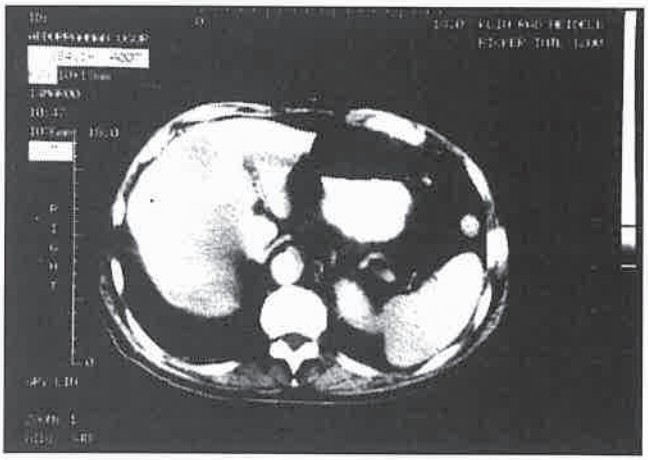

Figure IV.

which has been reported (2,3,6,8) was not discussed.

We believe that the technique of cardiopulmonary bypass and deep hypothermic circulatory arrest represents a significant advance in the management of renal tumors with extensive thrombi involving the inferior vena cava.

The advantages of this technique include;

(a) elimination of the need for extensive dissection of the inferior cava in order to obtain proximal and distal control;

(b) obviation of occlusion of major vessels with the attendant risks of warm ischemia, hypotension and hemorrhage;

(c) up to 60 minutes of safe operative time in a bloodless field;

(d) complete visibility of the interiior of the vena cava with less risk of hemorrhage and distal tumor embolization;

(e) facilitation of thrombus removal by atriotomy;

(f) simultaneous completion of adjunctive procedures.

Most importantly, application of this technique in selected patients with otherwise locally confined tumors can result in meaningful long-term survival.

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CLINICAL EVALUATION OF TOTAL PARENTERAL NUTRITION: THE ALL IN ONE (TPN-AIO) ANALYSIS OF 64 PATIENTS

M. Barlas • A. Naycı • R. Konkan • MY. Mecdel • M. Çakmak • F. Özgüner • H. Dindar • H. Gökçora • S. Yücesan*

SUMMARY

If normal oral nutrition is difficult or impossible to maintain, essential nutrients may provided either by tube-feeding or by the intravenous route. Intravenous feeding should be utilized to only when oral-tube feeding are impossible.

The conventional administration system of Total Parentally Nutrition (TPN) often requires multiple bottles and two administration sets with the addition of electrolytes, trace elements and vitamins in the ward. These make heavy demands on nursing staff and restrict patients mobility. For each addition and the change of the bottle increases the risk of error, contamination and sepsis.

The combination of parenteral amino acids, dextrose and lipids in one container has become known as an "all in one" "3 in 1" "triple mix" or a total parenteral nutrition admixture (TPN-AIO).

This kind of use of TPN-AIO was started in our clinic after an experimenthal study (invitro-invivo), in newly hatched hesix chicks (1).

The medical records of 64 patients at the Pediatric Surgery Department of Ankara University who were a day to 13 years of age received TPN-AIO were reviewed.

There were 38 (60%) newborns (24 male, 14 female), ten (15%) infants (7 male, 3 female) and sixteen (25%) children (11 male, 5 female). Thirty seven (58%) patients received only central, fifteen (24%) peripheral vein and twelve (18%) peripheral plus central vein.

We conclude that the three in one method of parenteral nutrition administration is safe, efficacious, and cost effective for pediatric patients.

Key Words: *Total Parenteral Nutrition All-In-One (TPN-AIO).*

These is a well known correlation between the operative nutritional status and the postoperative morbidity and mortality. Due to this fact, perioperative nutritional therapy has gained growing importance.

The combination of parenteral amino acids, dextrose and lipids in one container has become known as "all in one" "triple mix" or total parenteral nutrition admixture (TPN-A).

The first nontoxic intravenous lipid preparation, intralipid, was developed in Europe during the early 1960s and gained acceptance in North America in the 1970s (17). Initally, intravenous lipid was administrated separately from the parenteral nutrition (PN) solution. However, in 1971 Sollassol et al in France began using PN solutions with the lipid mixed in the same bag as the dextrose and amino acids (20). According to the distributors of intralipid, it is estimated that approximately 38% of the hospitals in the U.S. (>200 beds) provide TPN-AIO to their hospitalized patients and the number is expected to increase to 45-50% by 1995 (5).

The introduction of TPN-AIO has offered several clinical advantages. Substituting a portion of the daily dextrose calories with lipids may reduce the incidence of carbohydrate-associated complications (e.g. disturbances in glucose control and immune function). In addition, providing intravenous lipids continuously over 24 hours as a TPN-AIO appears to be better utilized by the liver and less likely to interfere with reticuloendotelial system function when compared wtih conventionally administered, discontinuous lipid infusions. If the peripheral vein is used as a route for parenteral nutrition, the addi-

* Department of Pediatric Surgery, Faculty of Medicine University of Ankara

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tion of fat the admixture provides the advantage of enhancing caloric density, while contributing significantly less tonicity than dextrose (1-5).

We reported here a retrospective study of 65 patients who was received TPN-AIO at the Pediatric Surgery Department of Ankara University.

MATERIAL AND METHODS

The medical reports of 64 patients at the Ankara University of Pediatric Surgery Department who received TPN-AIO were reviewed. Age range was 1 day to 13 years. 42 (65%) patients were male, 22 (35%) were female. There were 38 (60%) neonates (24 male and 14 female), 10 (%15) infants (7 male and 3 female) and 16 (25%) children (11 male and 5 female). The average birth weight were in 38 (60%) newborn 2573.4g (1000-3800 g), in ten (15%) infants 4249.0g (1790-8000g), in sixteen (25%) children 17781.2g (7500-27000g) The diagnosis of 64 patients were shown in table 1.

TPN-AIO was started with 10% dextrose, 6% trophamine or 10% aminosteril and 10% lipid solution admixtures with daily NaCL+KCL, vitamine and heparin (1U for each ml of TPN-AIO). The admixtures "three in one" were prepared daily and in sterile manner. Lipid solution was started mostly 0.5-1 ml/kg and was continued for "nice to meet lipid for endothelial receptor" for two days.

Table 1: Diagnosis of TPN-AIO Administered 64 Patients

Diagnosis	
Apple Peel Syndrome	1
Congenital Aganglionic Megacolon	7
Intestinal Atresia	3
Malrotation	1
Intestinal Stenosis	1
Chalasia	2
Meckel Diverticula	2
Gastrochisis	5
Omphalocele	6
Duodenal Atresia	1
Esophageal Atresia + Tracheoesophageal Fistula	8
Neonatal Necrotizing Enterocolit	7
Annular Pancreas	1
Anorectal Atresia	2
Esophageal Web	1
Hepatocellular Carsinoma	1
Choledocal Cyste	1
Plastrone Appendicitis	4
Gastrointestinal Hemorrhagie	2
Sacrococygeal Teratoma	2
Meconium Peritonitis, Meconium Ileus	4
Brid Ileus	2
Total	**64**

The peripheral or central vein route administration of TPN-AIO was depended on the consantration (table 3). The used route for the TPN-AIO that administered to 64 children were, 37 (58%) central vein infusions, 15(24%) peripheral vein infusions and 12 (18%) peripheral+central vein infusions.

Total duration time of TPN-AIO was 488 days for 64 patients. The least time was 1 day and the longest time was 23 days.

Biochemical parameters were checked in classic manner. In critical ill patients it depended on the status, but if the patients general condition was good we prefered daily body weights, urine sugar, but if the patients general condition was good we prefered daily body weights, urine sugar, aceton and plasma turbidity, twice weekly complete blood and urine count, weekly blood sugar, liver functions, renal functions, electrolites, total protein and bilirubin levels.

RESULTS

The weight were found in 25 (65%) newborns, in 4 (40%) infants, and in 9 (56%) children (Total 38-60% patients).

There were not any complications in 51 (80%) patients. The complications found in 13 (20%) patients were: 6 sepsis, 2 lipid embolies, 2 embolies, 2 hyperglycemias, 1 flushing and 2 glycosurias. Lipid emboly was due to accidentally faster infusions of TPN-AIO. There were not any mortality due to these complications (table 4). The cause of mortality were mostly due to multiple malformations, low birth weight and sepsis. Associated anomalies were in 28 (40%) of 64 patients (table 2).

DISCUSSION

A daily supply of energy is necessary in an optimal state of nutrition to offer the best resistance to illness and trauma such as infection, burn, surgery etc. It has long been recognized that there is a relationship between nutritional status and postoperative morbidity and mortality.

Seitzer reported that patients who had preoperative serum albumin levels below 2.5 g/dl had postoperative complications and sixfold greater mortality than patients with serum albumins above 2.5 g/dl.

Table 2: Associated Malformations of TPN-AIO Administrated 64 Patients

Malformation	
Total Intestinal Aganglionosis	1
Internal Hernia	2
Malrotation	4
Situs Inversus + VSD + Pulmoner Stenosis	1
KAM	2
NNEC	1
Apple Peel Syndrome	1
Multiple Intestinal stenosis	1
Omphalocele Rupture	2
ARDS	2
Brid Ileus	2
Henoch Schönlein Purpura	1
Meckel Diverticula	1
Intestinal Perforation	1
Lung Metastase	1
Atelectasia	1
Meconium Plug	1
Rectum Duplication	2
Meconium Peritonitis	1
Total	**28**

It is not unexpected since depression of the immune system is associated with malnutrition. This emphasized the fact that poor nutritional status can result in poor operative prognosis (19).

The conventional administration system of TPN with parallel lines often requires multiple bottles and with the addition of electrolites, trace elements and vitamines in the ward. These makes heavy demands on nursing staff and restrict the patients mobility. For each addition and the change of the bottle increases the risk of error, contamination and sepsis. Administration of single admixture of the components used in total parenterally nutrition "TPN-AIO" has been considered more convenient (3-10).

If pumps are absent (like as in undeveloped countries) or not used, the rate of administration of fat emulsion via "Y" connector is difficult to control. The use of a double 4 site is not always easy or even possible particulary in small tiny babies.

The combination of parenteral amino acids, dextrose, and lipids in one container has become known as a "all in on" "3 in 1" "tripple mixe or a total parenteral nutrition admixture (TPN-A).

1971 Solassol et al in France began using PN solutions with lipid mixed in the same bag as the dextose and amino acids (20). Such admixtures have been extensively used by Solassol and coworkers since 1972, by Kleinberger since 1976, in a limited way by Jacobson et al, and recently by Burnham et al (20). Solassol et al have used mixtures of all nutrients in one single bottle without observing any toxicity or adverse effects. Solassol and co-workers reported new techiques for long-term intravenous feeding. Portable models of the complete mixture is contained in a two-liter or a one liter scurasil sac with the pump on the waist belt. They used these techniques in 75 patients with minor complication (20). This concept of a total nutrient admixture or a three in one solution was soon being advocated for its simplicity and efficiency of use. In the United States, acceptance of the three in one solution was slow due to questions of catheter occlusions and solutions stability (dispite continued manufacturer of intralipid) (5.18.21.23).

The incorporation of lipids with amino acids and dextrose in one container offers benefits over the use of conventional amino acid-dextrose admixtures. In general, this practice has fostered the use of lipids as a daily caloric source and may avert the problems associated with excessive dextrose administration, particulary during critical illness. Moreover, incidences of adverse reactions and effects occur more with discontinuous lipid administration. On the other hand, continuous lipid administration through improved metabolic utiliza-

Table 3: Route of TPN-AIO Administrated 64 Patients

Route	
Peripheral Vein	15 (23.4%)
Central Vein	37 (57.9%)
Peripheral + Central Vein	12 (18.7%)
Total	**64 (100%)**

Table 4: Complications of TPN-AIO Administrated 64 Patients

Complication	
Sepsis	6
Lipid Emboly (Lung)	2
Hyperglycemia (>300 mg/dl)	2
Glycosuria (++++)	2
Flushing	1
Total	**13**

tion may reduce the incidence of these reactions (2. 11-15).

Rollins et al reported in 1990 that three in one parenteral nutrition was a safe and economical method of nutritional support for infants. They concluded that the two plus one system cost 11.78 D more per day than the three in one system. Nursing time is not included in the cost estimations. Inclusion of nursing time would increase the cost associated with pump maintenance and replacement are not included in the cost calculations. Such costs would be twice as much for the two plus one solutions compared to the three in one solutions, since twice as many pumps are used for the two plus one solutions (17).

Keefe et al reported in 1985 that in 85 consecutive general hospital patients requiring TPN were prospectively studied in order to evaluate the safety and efficacy of a 3 in 1 nutrient mixture. All formulas were individualized to estimated requirements mixed in the hospital pharmacy contained within 3 liter EVA plastic bags and given to the patients as a continuous 24 hours infusion. The average duration of TPN was 19 days per patient (range 8-24 days). Deposition of lipids on the internal surface of catheter was a common problem after 2 weeks continuos administration. Temporary problems with faulty common problem after 2 weeks continuos administration. Temporary problems with faulty bag connections resulted in excessive catheter sepsis (14%) due to Staphylococcus epidermidis. Mild reversible disturbances in liver function occured in one third of the patients. The system appears safe and effective for the management of most patients requiring long term TPN (15).

Likewise the all other authers and with our experimental study, we believed that the TPN-AIO is safe, cost effective efficacious and more suitable for our country.

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MANAGEMENT OF CHRONIC DROOLING WITH BILATERAL SUBMANDIBULAR GLAND EXCISION and BILATERAL PAROTID DUCT LIGATION

Sarper Yılmaz* • Kutlu Sevin** • Oğuz Yenidünya*** • Erol Demirseren* • Gökhan Adanalı*

SUMMARY

Chronic drooling is an important problem both for the patient and for the family. The problems of drool are social, physical and psychological. The control of chronic drooling has been difficult in the past. Nonsurgical treatment modalities are not practical and satisfactory. Previously, the most popular treatment method was the Wilkie procedure in which the salivary flow was diverted from the parotid glands by means of surgically created tunnels to the tonsillary fossa, along with submandibular gland resection. Submandibular gland resection with bilateral parotid duct ligation is an alternative technique. We operated three patients with chronic drooling using this technique. No serious complications occurred but only mild postoperative swelling in the parotid region was noted.

Key Words: *Drool, Cerebral Palsy*

It is estimated that 5 in every 1000 children born have a motor deficit compatible with cerebral palsy. Fortunately, only 10 to 20 percent of these children are severely handicapped (1). Drooling is frequently associated with neurologic disorders, such as cerebral palsy, Parkinson's disease, myasthenia gravis, facial paralysis, demyelinating diseases, vascular occlusion, cerebral injury and radical carcinoma surgery (2,3). Major concern about the chronic drooling patient group is the cerebral palsy group. In those patients orofacial motor control and swallowing mechanisms are disturbed. This creates a troublesome hygienic problem for these patients and frequently necessitates wearing a bib throughout the day. This problem may be emotionally disturbing to many of these patients.

Management of drooling has been attempted using drugs, radiation, transtympanic neurectomy and direct surgical intervention. Drugs and radiation therapy have had limited and poor results (4,5). In transtympanic neurectomy, chorda tympani and tympanic nerves are exposed in the middle ear and transected under direct vision (6,7,8,9). The resultant loss of taste sensation is a very significant disadvantage. Regeneration or aberrant routes seem to take place to diminish the long term results of reduction in drooling (10).

In 1964, Wilkie reported the bilateral submandibular gland resection and bilateral repositioning of the Stensen's duct into the tonsillar fossa (11). Brody became associated with Wilkie and together they amassed the largest series of cases (12). This mode of treatment has remained standard since its inception in 1964. However, major criticisms of this procedure include its technical difficulty, the development of parotid duct fistula and prolonged hospitalization.

Parotid duct ligation has been advocated to treat chronic parotitis, salivary fistula and drool (2,3,4,13). Atrophy of the gland substance has been shown experimentally by Wallenborn (14). Dundas and Peterson in 1979 and Brown et. al in 1985 presented series of 14 and 10 patients, respectively, who underwent bilateral submandibular gland excision with bilateral parotid duct ligation (15,16). Both groups reported good to excellent results in 75 percent of their patients. Recently Brundage reported the largest series of 58 patients who underwent the same procedure with a success rate of 86 percent (good to excellent results)(17).

* Resident in Plastic and Reconstructive Surgery, Ankara University Faculty of Medicine
** Associate Professor in Plastic and Reconstructive Surgery, Ankara University Faculty of Medicine
** Assistant Professor in Plastic and Reconstructive Surgery, Selçuk University Faculty of Medicine

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Guerin has introduced another variation, a three stage procedure which includes Wharton duct reposition (18).

METHODS

We present three cases with chronic drooling operated in our institution. All procedures are performed by the same surgeon. None of the patients had been previously operated for this specific problem. The first patient had cerebral palsy, the second one had tuberculous meningitis sequel with fairly well mental status. The third patient had suffered from facial paralysis, but he had a very poor oral control which leads to drooling.

Surgical Procedure

The procedure was performed under general anesthesia. Bilateral submandibular incisions were used. The submandibular glands were excised, taking care of all surrounding neural structures including the hypoglossal nerve, the lingual nerve and the marginal mandibular branch of the facial nerve. Following the excision, hemostasis was obtained and wounds were sutured and closed with penrose drains. A mouth gag was then inserted, and each parotid opening was identified and cannulated. An elliptical incision was carried out around the opening of the duct. The Stensen duct was dissected for about 5 mm and suture ligated. The buccal mucosa was then repaired with catgut sutures..

Results

Results of drooling control were classified using the same criteria as used by Wilkie and Brody (17):

1. Excellent: Normal salivary control
2. Good: Slight loss of saliva with or without dried froth on the lips
3. Fair: Improved with significant residual saliva loss or with thickened, offensive, brown, gummy froth.
4. Poor: Failure to control or too dry.

During the early postoperative period, marked swelling in the parotid region was treated with antihistaminic drugs and soft diet. The family of the first patient was satisfied very much with the result of the operation. The need for hourly dressing change reduced to one or two times daily.

Table I : The patients' clinical data

patient number	age	diagnosis	complication	result
1	4	cerebral palsy	preauricaular swelling	Good
2	2 years	tuberculosis meningitides sequel	late postoperative submandibular swelling	Good
3	25 years	facial paralysis	-	Fair

The second patient who had a problem in oral control due to tuberculosis meningitis sequel had a normal mental development and was a successful student in the secondary school. He was very motivated to have an operation with his problem. Two months after the operation he consulted us with a painful swelling in the submandibular region. There was no sign of infection. He responded very well to antiinflammatory drug medication.

The third patient had a severely defective oral control due to facial paralysis sequel which improved after the operation. Although his oral control was improved postoperatively, the result was only "fair" because of the severity of the oral control deficit.

The average duration of follow-up was 1 year.

DISCUSSION

Chronic drooling is a very important social problem both for the family and for the patient. Since Wilkie first reported his method for surgical treatment of drooling in 1964, it has become the standard mode of therapy. However because of the technical difficulty and the high rate of cyst and fistula formation, some authors advocate bilateral parotid duct ligation along with the bilateral submandibular gland excision (3,4,7,9,19). This technique is relatively easy and less time consuming (1 hour). We did not observed any serious complications in our patients. This is a safe and useful technique and is an important attempt to improve the disturbed social relationships of the patients.

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AN EXPERIMENTAL EVALUATION OF GUIDED BONE REGENERATION IN RAT TIBIAS

Reha Kişnişçi* • Serpil Duran* • Funda Tuğcu* • Esra Erden**

SUMMARY

Guided Tissue Regeneration (GTR) has been developed in order to provide a mechanical prevention of connective tissue ingrowth into bone defects by a membrane technique. In this study we aimed to compare the healing of through and through defects with monocortical versus bicortical placement of expanded polytetrafluoroethylene membranes. We also aimed to investigate the effects of intact periosteum on bone healing because periosteum is usually considered to act as a provider of progenitor osteogenic cells for osteogenezis. We used twelve rats and examined the healing of through and through defects created on both of their tibias. Histological evaluation showed better and advanced bone healing in membrane covered defects than in control group. However only slight differences were observed between the monocortically and bicortically membrane covered defects. This is attributed to the intact periosteum which served as a natural membrane on the uncovered side.

Key Words: *Guided bone regeneration, bone healing, Polytetrafluoroethylene membrane*

Regeneration of bone defects occuring as the result of cysts, infection, tumors, trauma or congenital malformations still remains a significant problem in oral and craniomaxillofacial surgery. The main hindrance for successful bone healing and the formation of new bone to occur, is a rapid formation of soft connective tissue. Numerous methods such as autogenous bone grafts and synthetic graft materials have been developed in order to provide an ideal bone substitute(1,2).

Guided Tissue Regeneration (GTR) has been developed in order to provide a mechanical prevention of connective tissue ingrowth into bone defects by a membrane technique. Thus a secluded space between the bone and the membrane into which cells exclusively originating from bone tissue can migrate is provided (1,3). This technique has proved successful results in the treatment of localized bone defects (4,5,6,7), in conjunction with dental implants (8,9,10,11), in reconstruction and augmentation procedures (12,13,14) and in periodontal surgery (3,4,15). Membrane technique has been reported to give successful results in the treatment of through and through jaw defects. Periosteal vascular bed acts as a provider of osteogenic cells for osteogenezis so it is very important in bone repair (4) and we aimed to investigate the effect of nonresorbable membranes and intact periosteum on wound healing. Therefore we designed this study to compare healing of through and through defects with monocortical versus bicortical placement of expanded polytetrafluoroethylene (e-PTFE) membranes.

MATERIALS and METHODS

Twelve rats (body weight 425 to 500 g) were used in this study. The animals were anesthetized by Ketamin HCL (0.1 mg/kg, Ketalar, Eczacibasi, Istanbul, Turkey) and a local anesthetic with adrenalin (Ultracain DS, Hoecsth, Istanbul, Turkey) was given at the site of surgery. After the medial aspects of both tibias had been shaved and washed with

* Department of Oral and Maxillofacial Surgery
** Department of Pathology, Medical Faculty of Ankara University
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Betadine solution, the skin incisions were made. Musculocutaneous layers were dissected followed by periosteal incisions on the anterior tibial aspect. A trephine bur was used to create similar, standardized, round, through and through osseous defects 5 mm in diameter on the anterolateral cortex of both of the tibias, being close to the epiphysis (Fig. 1). The defect on the right tibia was covered monocortically and the defect on the other tibia was covered bicortically with nonbiodegredable e-PTFE membranes (Gore-Tex; W.L. Gore and Assoc., Flagstoff, A.Z.). In the monocortically placed membrane group free edges of the membranes were tacked in between bone and periosteum to partly wrap tibia anteriorly, posteriorly and laterally whereas in the bicortically placed membrane group membranes were wrapped around tibia to meet free edges together. The flasp including the periosteum was carefully repositioned on the outer side of the membrane and sutuder. A control group was also developed with no membranes over the defects. The animals were divided into there groups including four rats in each and the healing was examined at the end of postoperative second, fifth and tenth weeks. The animals were killed with an overdose of Penthobarbital. Specimens were obtained comprising the defect region and they were fixed in % 10 formalin and decalcified in % 10 formic acid solutions. All animals sacrified in different time periods showed intact membranes covering bony defects. These membranes were not found valuable for microscobic examination. Serial 6 micron horizontal section were made, stained with hemotoxylin eozin and photomicrographs were taken. Inflamatory response, presence of fibrous tissue and cartilage and formation of osteoid, woven and lamellar bone were recorded in the histological examination.

The experimantal outline was in compliance with the regulations of Animal Research Laboratory of Ankara University, Turkey.

RESULTS

Two Week Specimen

Defects with bicortical membranes showed fibrous tissue formation together with cartilage and also osteoid in some region (Fig. 2). Around the edges of the defect these osteoid areas showed new bone formation.

The defetcs monocortically covered with e-PTFE membranes showed similar histologic findings with bicortical ones except for the more frequent occurrence of cartilage tissue (Fig. 3).

Control defects showed osteoid and cartilage besides fibrous tissue and in some of the cases inflammatory cell infiltration were also observed (Fig. 4).

Five Week Specimen

In the defects with bicortical membrane coverage transformation from cartilage to bone was observed (Fig. 5). A scenery of woven bone was persistent in the defects.

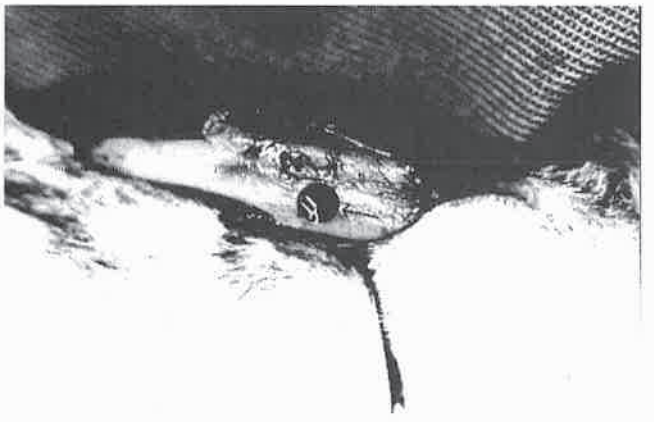

Figure 1- Standardized through and through defects created on the anterolateral aspects of rat tibias.

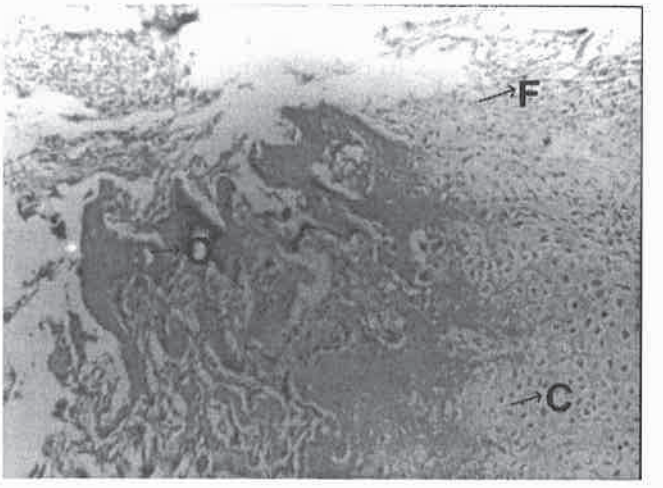

Figure 2- Fibrous tissue (F) formation together with cartilage (C) and osteoid (O) in two week specimen with bicortical membranes H.E.X. 100.

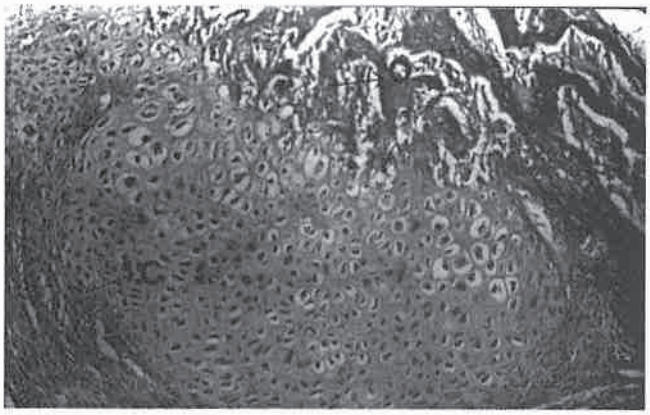

Figure 3- Osteoid (O) and cartilage (C) in two week specimen with monocortical membranes H.E.X.100.

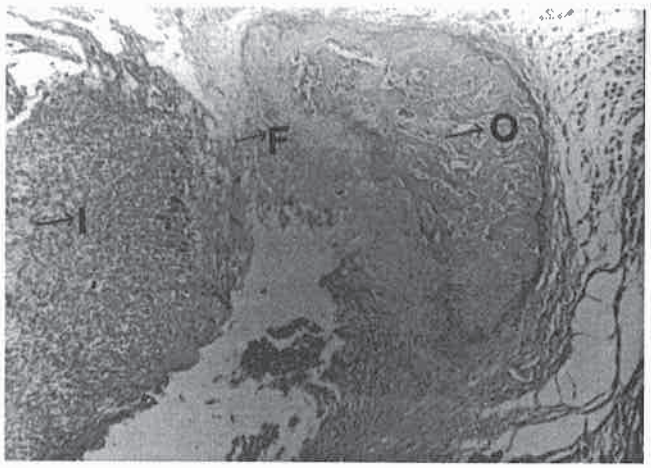

Figure 4- Control defects in two week specimen showing fibrous tissue (F), osteoid (O) and inflammatory cell infiltration (I) H.E.X. 50.

In monocortically covered defects cartilage and woven bone formation were observed besides fewer fibrous tissue (Fig. 6).

In control defects dens fibrous tissue was seen with some areas showing transformation to cartilage and woven bone (Fig. 7).

Ten Week Specimen

All defects were filled with lamellar bone in both mono and bicortical membrane groups (Fig. 8).

However fibrous tissue and osteoid was still consistent in control defects (Fig. 9).

DISCUSSION

Osteopromotive membrane technique has been proved to stimulate the healing of bone defects and regenerate new bone over the previously existing bone (14). Although these membranes are known to be osteoconductive some investigators have reported that they are also capable of creating new bone at sites where bone normally is not present (14,16). The inert membrane used mechanically prevents the invasion of soft connective tissue cells into the bone defect, while because of its pore size, still allowing free diffusion of tissue fluid and nutrients. Membrane coverage may also primarily reduce long term resorption by enchanced early incorporation of the grafts(17).

The amount of bone neogenesis has been found to be dependent on membrane qualities such as stiffness, porosity, the length of healing period and the width of the space (2,4,14).

Practical details such as the adequate formation

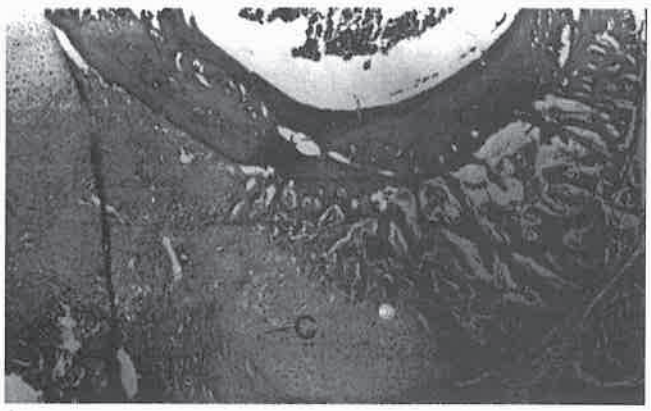

Figure 5- Transformation from cartilage (C) to bone (B) in monocortical membrane groups of five week specimen H.E.X 40.

Figure 6- Cartilage (C), woven bone (W) and fibrous tissue (F) in bicortical membrane groups of five week specimen H.E.X 100.

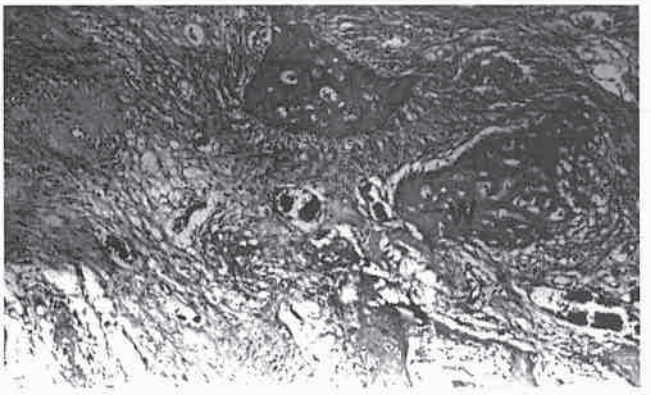

Figure 7- Control defects of five week specimen with fibrous tissue (F) and woven bone (W) H.E.X. 100.

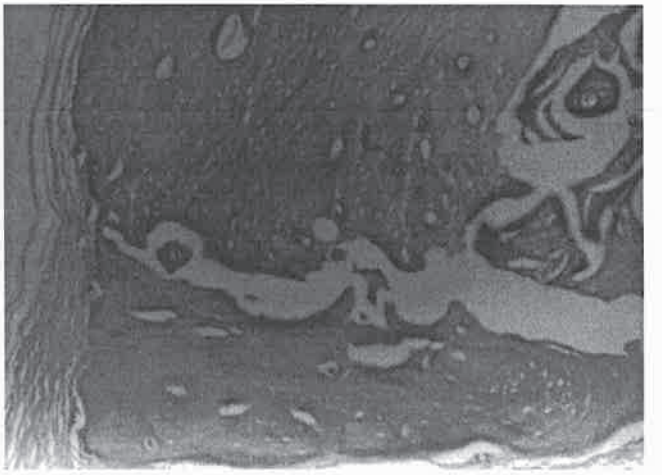

Figure 9- Fibrous tissue (F) still observed in control defects of ten week specimen H.E.X. 100.

of blood clot, maintenance of the space to be filled with osteogeneic cells and preservation of granulation tissue and vascular construction during the organization of hematome seem to be important in GTR (2,14,15,18).

Complete healing of membrane covered mandibular defects in rats (4) and in conjuction with implants in rabbits were reported to be 6 weeks and 8 week in dogs (8). Complete healing was observed after 12 weeks in monkeys (6). The longest healing period was reported to be 16 weeks in a study on the calvarial bone surface in rats. However active osteogenesis was still reported to be present, clearly indicating a need to increase the healing period even further for optimal results (14).

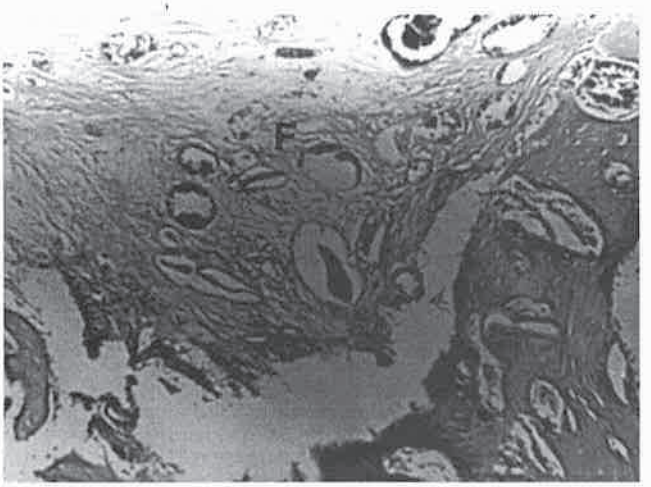

Figure 8- Lameller bone (L) farmation in both monocartically and bicortically membrane covered defects of ten week specimen H.E.X 100.

Membrane covered defects in our study showed woven bone formation at the postpoerative 5th. week and lameller bone at the postoperative 10th. week suggesting still the necessity of a longer period for complete ossification charecterized by cancellous and cortical bone remodelling (18).

PTFE membranes are well tolerated and its biocompatability is demonstrated by the almost total absence of a foreign body or inflammatory reaction (4,12) . The material was not observed in the lymph node (12).

Occurence of bone formation on the peripheral side of the membranes may probably suggest the osteoconductivity of the membrane itself. It was reported in a study that the mandibular bony lesions failed to heal without bilateral membrane coverage (17). In our study we observed only slight differences between the monocortically and bicortically membrane covered defects. The periosteum is usually considered to be a provider of cells of the osteoblastic lineage (14,15). Periosteum acts as a provider of progenitor osteogenic cells for osteogenesis (15,20) and may also function indirectly as a barrier membrane excluding nonosteogenic extraskeletal tissues from the organizing clot (15). In this aspect we may suggest that in monocortically membrane covered defects the intanct periosteum served as a natural barrier on the uncovered side.

It should be realized that the procedures based on this principle result in the regeneration of the body's own local bone (2,4). Thus this treatment concept opens new avenues in oral and maxillofacial surgery.

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ANOMALOUS ORIGIN OF THE RIGHT CORONARY ARTERY FROM DISTAL LEFT CIRCUMFLEX

Sinan Aydoğdu* • Murat Özdemir* • Erdem Diker** • Sengül Çehreli* • Ercan Varol* • Şule Korkmaz* • Emine Kütük*

SUMMARY

This report describes a patient with Lipton classification L1 form of single coronary artery where the right coronary artery originated from the distal circumflex and follows its usual course there after. With lesions involving the LAD and the circumflex artery which gave rise to the right coronary artery, there was significant 3-vessel involvement in this 69 years old patient who had undergone coronary artery by-pass surgery 15 years ago and was still alive. This rare anomaly seems to be a benign one with a favourable prognosis most of the time.

Key words: Coronary angiography, single coronary artery

Single coronary artery is very unusual in the absence of accompanying anomalies of the heart great vessels. It has been reported to occur in only. 0.024% of the population as an isolated finding(1). Here, we report a case with a rare form of single coronary artery and no accompanying cardiac malformations in which the right coronary artery originates from the distal left circumflex coronary artery.

Case report

A 69 years old male patient admitted to the clinic with the complaint of angina on effort. He had undergone coronary artery bypass graft surgery in 1981 and received an Ao-LAD-D1 sequential and an Ao-OM1 individual saphenous vein graft. He was symptom-free until 2 months ago when he developed angina on effort. The physical examination was normal except for a loud S4 gallop. The ECG was consistent with chronic anterior myocardial infarction. The cardiothoracic ratio was elevated in the chest X-ray. The echocardiographic examination was normal except for apical dyskinesis in the left ventricle. The patient underwent left ventriculography, coronary and saphenous vein by-pass angiography with the Sones' technique. The left ventriculography disclosed apical dyskinesis. Despite prolonged trials, the right coronary artery could not be catheterized selectively and a radiopaque injection into the right coronary sinus disclosed the absence of the right coronary ostium. Selective left circumflex coronary artery, beyond the crux of the heart, was seen to continue as the right coronary artery and follow retrogradely the usual right coronary artery course (Fig. 1). The left anterior descending artery was totally occluded after the origin of the first diagonal artery. There was a 90% stenosis in the first diagonal branch and a 70% stenosis in the circumflex artery after the first obtuse

* Türkiye Yüksek İhtisas Hastanesi, Cardiology Department, Ankara, Turkey.
** Ankara University, School of Medicine, Cardiology Department, Ankara, Turkey.

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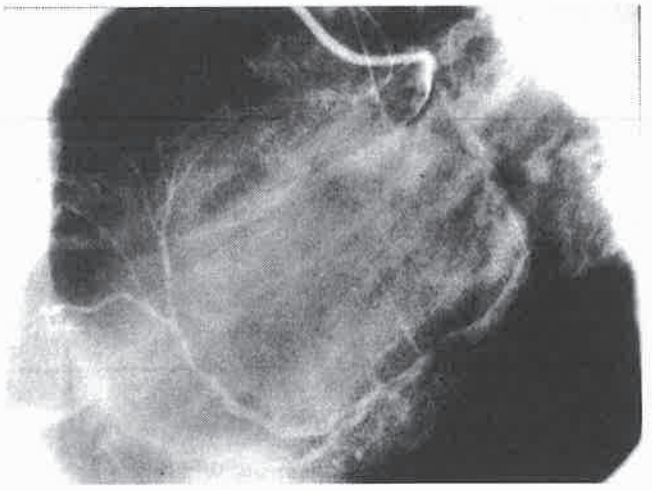

Figure 1- Left coronary angiogram in the LAO projection. The left circumflex artery continues beyond the crux as the right coronry artery.

marginal branch by visual estimate. The Ao- LAD-D1 sequential sapheous by pass graft was patent but the graft to the circumflex artery was found to be occluded. The patient was decided to be kept under medical therapy and discharged thereafter.

Discussion

Single coronary artery is usually associated with other congenital cardiac malformations. It is extremely rare as an isolated finding. The case presented in this report had no associated congenital cardiac anomalies. Single coronary artery has been classified into 9 categories by Lipton et al(1). According to this classification, L1 from involves single coronary artery which arises from the left coronary sinus and gives off the anterior descending and circumflex branches, then the circumflex artery continues across the crux of the heart as the right coronary artery.

Yamanaka et al have reported 20 cases with L1 form single coronary artery in their series of 126595 patients undergoing coronary angiography (2), but these cases are not detailed in their paper. Until now, there has been 6 cases with this form of coronary artery anomaly precisely defined and detailed by cardiac catheterization(1,3-7).

Although there has been reports of sudden death in cases with single coronary artery where the artery traces between the aorta and the pulmonary artery may be regarded as a benign anomaly. Our patient was 69 years old, he had undergone coronary artey by-pass surgery 15 years ago and was still alive.

In 5 of 7 cases reported including ours, there was arterosclerotic coronary artery disease in conjunction with single coronary artery abnormality. Although it has been reported that single coronary artery may cause accelerated atherosclerosis, this issue is not settled yet(1). *The high prevalence of atherosclerosis in cases reported till now does not allow us to say that single coronary artery pedisposes to atherosclerosis because all the patients are symptomatic.* In our case, LAD was totally occluded and there was significant lesions in the diagonal and proximal circumflex coronary arteries. Considering that the right coronary artery originated as a continuation of the distal left circumflex, there was significant 3-vessel disease in our patient.

In L1 form of single coronary artery, if the LAD does not cross the apex and there is a critical stenosis in the body of the left circumflex and if this lesion is suitable for percutaneous transluminal coronary angioplasty (PTCA), it might still be wise to consider PTCA a high risk procedure since occlusion of the angioplasty site due to dissection or thrombus could compromise blood flow to a significant amount of myocardium. But Bathe et al have successfully applied PTCA to such a case (7).

In conclusion, cardiologists should be able to identify rarely occurring coronary artery anomalies like this in order to perform accurate evaluation and avoid subsequent errors in patient management.

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HEPATITIS C VIRUS RELATED POLYARTHRITIS

Mehmet TOSUN* • **Turan USLU*** • **Mustafa GÜLER*** • **Şenol ERDOLU*** • **Nadir HANSU***

SUMMARY

We have described a patient who developed hepatitis C virus (HCV) related polyarthritis which was diagnosed by the presence of antibodies against HCV by second generation ELISA and later confirmed by percutan liver biopsy. Acute arhtritic symptoms were alleviated with prednisolone, but arthralgia and elevated liver enzymes and anti-HCV antibody positivity have persisted for one year period. Following the a-interferon treatment, while liver enzyme levels returned to normal range and anti-HCV antibody became negative, arthralgia has persisted throughout.

Key words: *Polyarthritis, hepatitis C virus*

Viruses have been considered as the etiologic factors in the development of rheumatic diseases. The association between HBV and arthritis has been well documented (1, 2). Recently, it has been realised that HCV hepatitis accounts for 7O % to 8O % of non-A, non-B hepatitis by the serological testing for hepatitis C (3, 4). Here, we report a patient who developed symmetrical, non-destructive polyarthritis after transfussion associated HCV infection.

Case Report

A 35 year-old man who presented on May 31, 1994 with a 3 week history of fever, generalised myalgia, severe pain and swelling in both large and small joints and morning stiffness lasting more than 2 hours. He was initially diagnosed as reactive arthritis developing after upper respiratory tract infection, and treated with penicilline and aspirin by a general practioner, but he saw no benefit from this treatment regime. In his past history, he had had upper respiratory tract infection 3 weeks prior to the admission and upper gastrointestinal bleeding 12 years before our evaluation and at that time he had received 4 units of blood. However, no jaundice was noted.

On admission, his general status was moderate and he was bound to a wheelchair. His temperature was 38.5°C, his pulse rate was 1O4 beats/minute and his blood pressure was 14O /8O mmHg. The features of systemic examination were normal. The evaluation of joints revealed severe pain and other arthritic signs in wrists, elbows, right MCPs, and PIPs, knees and ankles. There was mild effussion in his knees. On laboratory investigation abnormal test results were as follows: WBC 14.3OO /mm3, ESR 1O4 mm / hour, the serum levels of SGOT 49 IU/L (7-40), SGPT 264 IU/L (7-35), GGT 184 IU/L (0-85), CRP +++, IgG 196O mg/dl (700-1500), C3 49.6 mg/dl (80-170). Serum anti-HCV IgG and IgM antibodies were found repetetively positive by second generation ELISA. All the other test results including Hb, Hct, Plts, other blood chemistry analysis, urine analysis, ASO, RF, Brucella, ANA, anti-ds DNA, IgA, IgM, C4 and Cryoglobulin were all in normal ranges. Serum HBsAg, anti-HBs antibody, anti-HBc antibody, anti-HIV antibodies were negative. The X-ray features of the chest and joints were normal. No microorganism was cultured in the blood, throat or urine samples. Histological evaluation of percutaneous liver biopsy specimens indicated to a chronic active hepatitis. Because of poor response to non-

* From the Department of Physical Medicine and Rehabilitation, Medical School of Karadeniz Technical University, 61080 Trabzon, TURKEY

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steroidal anti-inflammatory drugs, oral prednisolone (0.5mg/kg /day) was started. A few days after, his symptoms alleviated dramatically. At the end of the second week, body temperature, all the inflammation signs and laboratory findings, except elevated liver enzymes and anti-HCV antibody positivity, returned to normal values. The dosage of steroid was tapered and subsequently stopped at the end of 6th week. During the tapering of the drug his complaints of arthralgia were pronounced again. Furthermore mildly elevated liver function tests and anti-HCV antibody positivity have persisted for one year. As subsequent liver biopsy specimens revealed a worsening damage in the liver, α-interferon treatment regimen with three million units per week was started . After six months use of interferon liver enzyme levels returned to normal ranges and serum anti-HCV antibody became negative. Nevertheless, arthralgia was noted to persist in an increasing fashion during and after the interferon treatment.

DISCUSSION

Rheumatic symptoms frequently occur in the course of viral hepatitis. Generally these symptoms first become apparent during the predromal period or at the onset of the clinical illness, and subside after the development of typical manifestations of hepatitis, resulting in no joint deformity (1, 2, 3, 4). There has been a single case report in which the patient developed progressive rheumatoid arthritis subsequent to acute hepatitis caused by hepatitis B virus (5). Since tests for the hepatitis C virus have become available, it is understood that HCV accounts for 7O % to 8O % of non-A, non-B hepatitis (3, 4). Several systemic and rheumatic manifestations and immunologic abnormalities related to HCV infection have recently been described . These rheumatic symptoms consist of arthritis or arthralgia, myalgia, sicca syndrome, rheumatoid arthritis, polyarteritis nodosa and lupus-like manifestations (2, 3, 4, 6, 7, 8, 9, 10).

There have been few case reports on HCV caused arthritis (2,3,4, 6, 8, 9, 10). It is generally symmetric, polyarticular and involves both small and large joints such as MCPs, PIPs, wrists, elbows, knees and ankles. Although arthritis is non-destructive in most of the cases, recent reports have implicated HCV as the trigger for development of rheumatoid arthritis (3, 4). Dhar et al. reported a patient with preexisting lupus developed a flare of her disease at the time HCV was diagnosed (8).

The immunologic abnormalities consist of cryoglobulinemia, the seropositivity of RF, ANA, anti-Ro antibody, anti-mitokondrial antibody, anti-smooth-muscle antibody, low titer ds-DNA, low complements and polyclonal gammapathy (2, 8, 9, 10, 11). The prevalance of RF may be high in HCV-infected patients due to viral-induced production of anti-IgG antibodies (12). In some cases hepatitis B and hepatits C are coexist (2, 13). Ilan et al. reported that dual infection rate of HBV and HCV was 66 % and these patients develop more serious complication than HCV alone (13). One might speculate that some of the patients with reported hepatitis B arthropathy could also have had coexisting HCV infection as the etiology of their arthritis. On the other hand there have been some reports of false positive HCV serology in patients with rheumatoid arthritis (2,14). Although Baffony et al claimed that anti-HCV antibodies found in rheumatoid arthritis are true positive based on findings with second-generation ELISA and immunoblots (14). We were not able to perform confirmatory tests including immunobloting or PCR. However the elevated liver enzymes and histologic features of biopsy materials in addition to positive serology obtained with using second-generation ELISA supported the diagnosis of chronic HCV hepatitis in our case. The mechanism of HCV hepatitis-associated arthropaty is unknown. The autoimmune mechanism might play the main role in the pathogenesis of the arthropaty. At the onset of the disease the virus-antibody immun complexes may be deposited in synovial tissues where activation of complement pathway can lead to an inflammatory response. Furthermore in some cases who demostrate persistant or latent virus infection, immuncomplexes can be formed locally in the synovial tissues, or a cellular cytotoxicity response may be generated to the viral antigens inserted in the synovial tissue cell membranes.

In conclussion, testing for HCV in patients with atypical or unclassified polyarthritis and showing abnormal or normal liver enzyme levels should be considered since some HCV positive patients may have normal enzyme levels at various times during the course of their illness.

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THYMIC CARDCINOID TUMOR: CONVENTIONAL RADIOGRAPHY COMPUTED TOMOGRAPHY, AND ANGIOGRAPHIC FINDINGS

Ayşe Erden* • Tuba Tekin Kızıltepe** • Mehmet Yurdakul* • Tülay Ölçer* • Turhan Cumhur*

SUMMARY

A 48-year-old woman with thymic carcinoid tumor was presented. The radiologic findings and differential diagnostic criteria of this rare entity were reviewed.

Key Words: *Thymus, neoplasms, carcinoid tumor, imaging techniques.*

Carcinoid tumors of the thymus are exceedingly rare. By 1972, fewer than 200 cases had reported in the world literature(3). There is close relationship between thymic carcinoids and endocrinopathies. When the tumor is not asssociated with an endocrine syndrome, as in our case, it may have symptoms and show signs of an anterior mediastinal mass(6).

CASE REPORT

A 48-year-old woman presented with palpitation, progressively increasing shortness of breath and chest pain of five years duration. Physical examination was normal except for a systolic murmur along the lower left sternal border (tricuspide area).

Laboratory findings showed Hb 12.8 gr/dl, WBC 8200/mm and the red cells are microcytis and hypochromic on the smear. The other routine blood and urine testing yielded normal results.

Posteroanterior and lateral chest roentgenograms demonstrated a lobulated mass of homogeneous density situated in the anterior mediastinal compartment and projecting to the left of the upper mediastinum (Figure 1).

Computed tomogaphy (CT) scans after intravenous (IV) contrast medium (CM), revealed a soft tissue mass sized 8x4 cm containing central necrotic areas (hypodense foci) adjacent to the aortic arch, main pulmonary artery and descending aorta (Figure 2).

Left subclavian angiography showed a hypervascular lesion whose blood supply was originated from internal mammarian artery (Figure 3 and 4).

Surgery revealed a soft mass extending to the left hilus over the pericard which had a close approximity to the aortic arch, descending aorta, and main pulmonary artery. It was partially covering the left phrenic nerve. The mass was totally resected by detaching its vascular connections.

Histopathologic examination showed the tumoral tissue consisting of the uniforme epithelial cells arranged in alveolar nests. Tissue revealed abundant vascularization with pseudo-rosette formation.

In the postoperative period, adjuvant chemotherapy was recommended by oncologic consultants.

DISCUSSION

Carcinoid tumors are of neuroendocrine origine, generally hormone-active tumors with a tendency to malignant degeneration. Eighty-five per cent of carcinoids occur in the intestinal system and

* Ankara Oncology Hospital Radiology Department
** Türkiye Yüksek İhtisas Hospital Radiology Department

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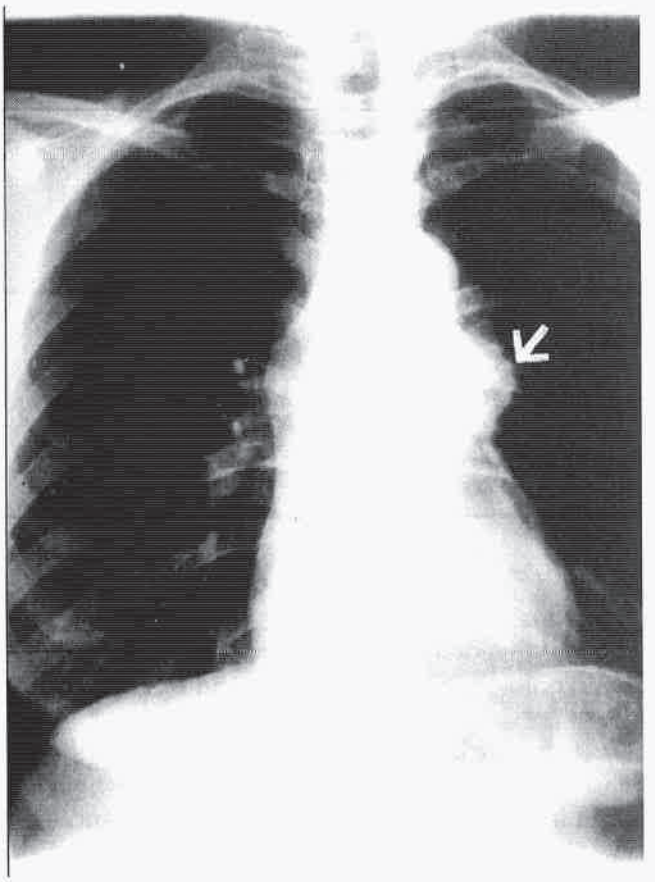

Figure 1. Posteroanterior chest roentgenogram shows a soft tissue mass (arrow) adjacent to conus pulmonalis.

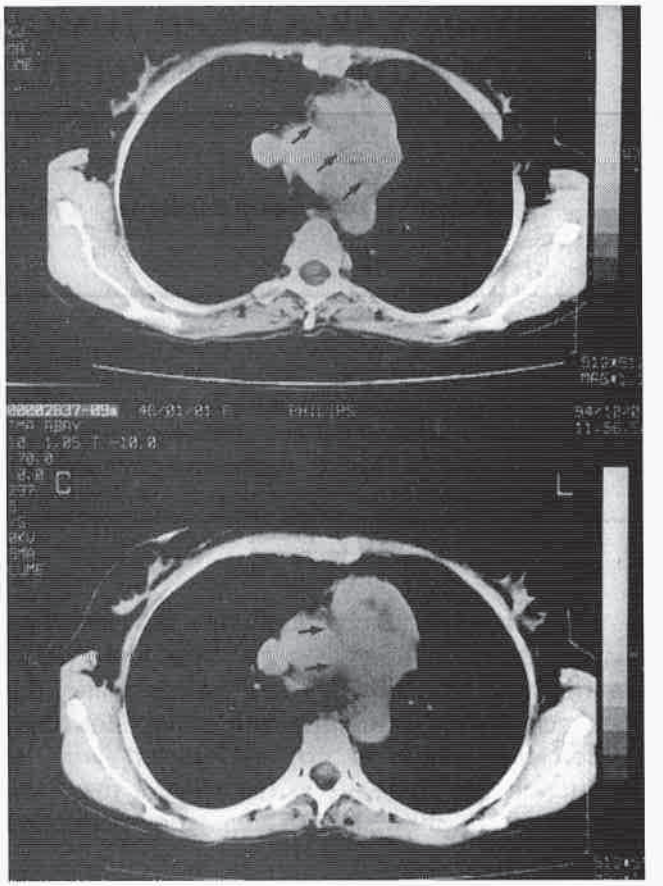

Figure 2. CT demonstrates the mass lesion (arrows) located anterior aspect of aortic arch.

ten per cent of them occur in the lungs. Rarely, they may arise in other sites including the esophagus, stomach, pancreas, biliary tract, ovary, and thymus. There appears to be a predilection for males(1).

Plain chest roentenograms are often normal but sometimes thymic carcinoids are visualized as a well-defined soft tissue mass near the junction of the heart and great vessels (1). CT scans reveal a soft tissue mass in the thymus location which shows patchy enhancement following IV CM. This technique is also useful for diagnosing early intrathoracic metastasis and thymus carcinoids may show hypervascularization while intestinal carcinoid tumors are known as hypovascular (4,7). In the literature, it was noticed that the blood supply of the thymic carcinoid tumor is from internal mammarian artery as in our case(5). Thoracotomy, with either biopsy or surgical removal is mandatory for accurate diagnosis (5). The radiologic imaging modalities so far available do not provide definite diagnostic evidence since, there is no specific sign for thymic carcinoids.

The other lesions arising from thymus gland such as thymoma, thymic cyst, thymolipoma should be taken into consideration in the differantial diagnosis of misdiagnosed as thymoma. Differentiation of these tumors is important as they have entirely different prognosis. Extrathoracic metastasis is the characteristic of thymic carcinoid. It can spread to skin, bone, lymph nodes and adrenal gland in 20-30% of cases. Although malignant thymoma can spread by implantation and by direct extension, distant metastasis are very uncommon(6). Invasion of adjacent thoracic tissues by thymic carcinoid is 80% and by thymoma is 10%. The prognosis of thymic carcinoid is poor since, it can metastase and show some degree of recurrence many years after the initial excision. Postoperative chemotherapy and radiotherapy may occasionally be of value although their roles are still uncertain. Prognosis is much more favorable in thymoma. The pathologic conditions associated with thymic carcinoids are Cushing's syndrome, MEA I (multiple endocrine adenomatosis), MEN II (Multiple endocrine neopla-

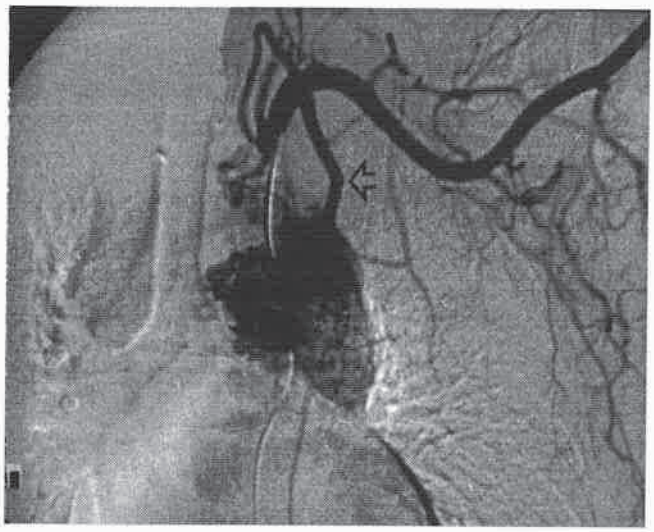

Figure 3. A hypervascular mass whose blood supply is originated from internal mammarian artery (arrow).

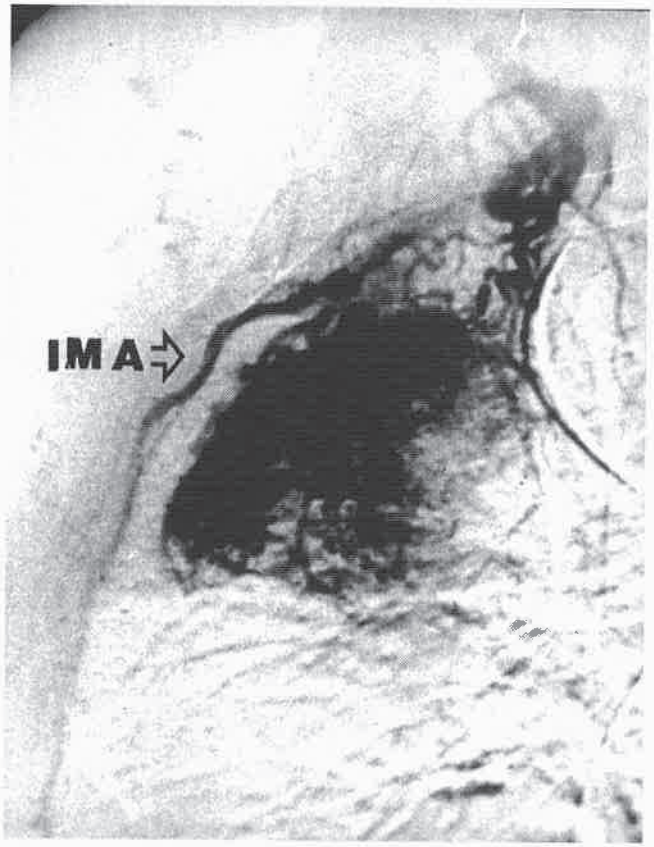

Figure 4. Lateral digital subtraction angiogram shows the anterior mediastinal location of the mass (IMA: Internal mammarian artery).

sia), inappropiate antidiueretic hormone (ADH) secretion, pericarditis, polyarthropathy, clubbing of fingers and myositis. On the other hand, thymoma may be associated with myastenia gravis, red cell hypoplasia or hypogammaglobulinemia (3).

The other thymic lesions -thymolipoma and thymic cyst- have benign characters. Typically, thymolipoma tends to cause few or no symptoms even when very large. The fat content of the mass can permit the preoperative diagnosis by CT examination. In thymic cyst cases, CT demonstrates a unit density close to water (0 Hounsfield Unit) thereby, effectively making the diagnosis. However, when hemorrhage has occured, thymic cysts may be indistinguishable from solid lesions and the differential diagnosis becomes wider(2).

Consequently, although rare, thymic carcinoids should be kept in mind in the differential diagnosis of anterior mediastinal masses. Even though long-term prognosis is poor, an aggressive surgical resection and adjuvant radiation therapy and/or chemotherapy may achieve lengthened survival with an excellent quality of life.

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SYSTEMIC SCLEROSIS ASSOCIATED WITH IMMUNE THROMBOCYTOPENIA AND PERNICIOUS ANEMIA

Güner Tokgöz • Nurşen Düzgün • Olcay Aydıntuğ • Taşkın Şentürk • Kenan Keven • Ümit Ölmez*

SUMMARY

It is known that immune thrombocytopenia is a rare disorder in patients with systemic sclerosis, unless it is complicated with Coombs positive hemolytic anemia, microangiopathy and D-penicillamine therapy.

We report here an interesting patient with systemic sclerosis presenting with pernicious anemia and immune thrmbocytopenia. A 63-year-old woman with systemic sclerosis was admitted to the hospital with diffuse purpura and petechial hemorrhage. As blood test revealed severe thrombocytopenia, slight megaloblastic changes and normal amounts of megakaryocytes were found on bone marrow examination. Prednisolone was introduced. However, thrombocytopenia partially responded to prednisolone, it was normalised after addition of danazol to her treatment. Vitamin B12 deficiency was determined and it was most likely the cause of her mixed bilateral peripheral polyneuropathy. Antiparietal antibody was found as positive.

To the best of our knowledge, this is the first systemic sclerosis case who had simultaneously autoimmune hematological diseases namely pernicious anemia and immune thrombocytopenia.

Key Words: *Systemic sclerosis, immune thromboyctopenia, pernicious anemia.*

Systemic Sclerosis (SSc) is a multisystem disorder of unknown etiology. Thrombocytopenia is a rare event in SSc (1-4). A patient with SSc in association with autoimmune hematological disorders, immune thrombocytopenia and pernicious anemia, is described in this report.

CASE REPORT

A 63-year-old woman was first admitted to the department of Immunology, Ankara University Medical School, Ibn-i Sina hospital, in 1994 for assessment of fever and cough. She had a long history of Raynaud's phenomenon of the fingers for which a thoracal sympathtectomy operation was performed in 1965. On examination, SSc was diagnosed on the basis of diffuse skin involvement, the esophageal and the pulmonary findings. She had dryness of the mouth and a gritty sensation in the eyes which was due to secondary Sjögren's syndrome. Esophageal radiography revealed the esophageal involvement with the gross evidence of aperistaltis. Electrocardiography and echocardiography were normal. A thorax CT and carbon monoxide diffusion study showed interstitial pulmonary involvement. Slightly high pulmonary pressure values were found in pulmonary hemodynamic study (35 mmHg systolic, 23 mmHg diastolic presure and 32 mmHg mean pressure). Urinalysis, renal functions and other bioschemical and blood tests were completely normal. The immunological laboratory findings are presented in Table 1.

She had been well until 3 months prior to her second admission to the hospital. She had severe hemorrhagic diathesis, and on history of medication except for nifedipine because of her hypertension. On physical examination, the blood pressure was 150/90 mmHg, the pulse was 90/minute. Thorax examination disclosed bilateral crepitant rales at the base of both lung fields. The patient had diffuse purpura and petechial hemorrhage, predominantly on the extremities. On the day of admission, platelet

* Medical School of Ankara University, İbn-i Sina Hospital, Department of Immunology, Ankara

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Table 1. Immunolocigal laboratory findings

ANA Pattern	(+++) speckled
Anti ds DNA (0-7.0 IU/ml)*	5.9
C_{3c} (0.5-0.9 g/L)*	0.87
C_4 (0.1-0.4 g/L)*	0.21
Anti scl 70(<25.0 Eu/ml)	Negative
Anticentromere antibody	Negative
Anti platelet antibody	Negative
Anti parietal antibody	Positive
Ig G (6.6-16.0 g/L)*	28.64
Ig A (0.45-3.50 g/L)*	3.71
Ig M (0.6-3.7 g/L)*	2.77
CD4 Lymphocyte (29-59 ")*	14
CD8 Lymphocyte (19-48 %)*	57
CD4/CD8 ratio (0.6-2.8)*	0.20

* Normal range

Table 2. Hematologic Laboratory Values.

	On Admission to the hospital	Three months after the treatment
Hemoglobin (glt)	8.6	12.5 g/lt
Hematocrit (%)	28.5	39.6 %
Mean corpuscular volume (μm^3)	92	85
Platelet count (per mm^3)	13000	226000
White-cell count (per mm^3)	9000	13200
Ferritin (9-120 ng/ml)*	87.2	Not repeated
Folic acid (2.7-17 ng/ml)*	10.2	Not repeated
B 12 (200-950 pg/ml)*	87.1	365.4 pg/ml

count was 13.000/ml and vitamin B12 level was low as shown by Table 2. There were normal numbers of megacaryocytes and slight megaloblastic findings in the bone marrow examination. Fecal hemoccult test, direct and indirect Coombs test were negative. Abdominal ultrasonography was normal. Prednisolone was started 60 mg daily. Platelet number increased slightly and stabilised around 40000 /ml after there weeks of prednisolone treatment. Normal platelet levels were achieved only after addition of 200 mg a day danazol to her daily prednisolone (Table 2). She had paresthesia and numbness on the lower extremities. Electroneuromyography revealed a mixed bilateral polyneuropathy. She was put on vitamin B12 replacement therapy. Hemoglobine level returned to normal level with this treatment and the patient was discharged with 102000/ml platelet numbers.

She was followed until July 1995 when progressive dispnea and pretibial eodema appeared. She was admitted to the hospital for assessment of severe pulmonary inffection determined on X ray and CT scan. Her blood pressure was 150/90 mmHg and pulse was 96/minute. She had bilateral crepitant rales at both lower lung fields. Interestingly, the patient's lymphocyte subgroups showed a very low CD4/CD8 ratio. HIV antibody was negative and there was no other cause of this abnormality. One week later, her respiratory failure worsened despite supportive, antimicrobial treatments and she died because of respiratory failure.

DISCUSSION

Thrombocytopenia is a rare disorder in patients with SSc (1-4). It is common practise to search for, when thrombocytopenia develops during the course of SSc, a microangiopathic syndrome related to scleroderma kidney, or less commonly an overlap with systemic lupus ertythematosis (SLE). Frayha et al, published hematological problems in their patients with SSc, and reported on 2 patients who had no appearant reason for thrombocytopenia (2). Natsuda et. al, reported a patient with SSc complicated with immune thrombocytopenia during D-penicillamine therapy(4). Kevin et al, published 2 patients with SSc associated with thrombocytopenia and Coombs positive hemolytic anemia. To the best of our knowledge, pernicious anemia and thrombocytopania have not been reported in associated with SSc previously.

An overlap with SLE would be a possible explanation for the thrombocytopenia, however, there was no finding to consider the patient as an overlap syndrome of SSc plus SLE.

The cause of vitamin B12 deficiency was accepted as pernicious anemia due to the presence of anti-parietal antibody. It was also most likely responsible for the mixed bilateral polyneuropathy. Severe vitamin B12 deficiency can be cause of thrombocytopenia, however, in this case, prednisolone treatment increased the platelet numbers before vitamin B12 raplacement therapy was introduced. Another cause of vitamin B12 deficiency in

patients with SSc might be involvement of the intestine. However, the patient did not have any absorbtion abnormality on stool examination.

It is reported that danazol is an effective and alternative treatmen for immune thrombocytopenia if it is resistant to prednisolone (5). In this case, thrombocytopenia was succesfully treated with danazol plus prednisolone because of failure to respond to prednisolone alone.

Although no association has been established between SSc, pernicious anemia and immune thrombocytopenia, considerable overlap can occur within the clinical course of the autoimmune hematological disorders in SSc. It can be incidental or the result of a common immunological pathogenesis.

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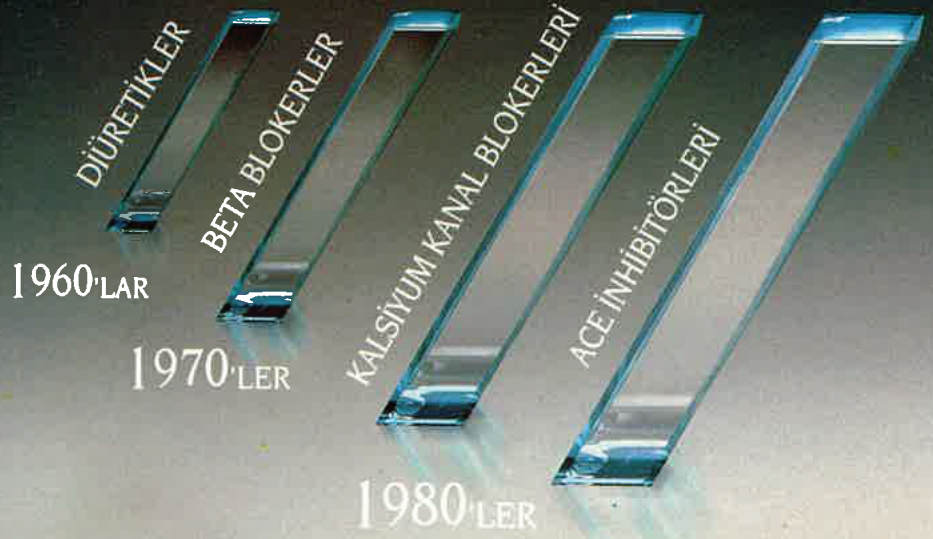
HİPERTANSİYON TEDAVİSİNDE SON 10 YILIN EN BÜYÜK KEŞFİ

YENİ BİR SINIFIN İLK ÜYESİ



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Ayrıca losartan bradikinin degrade eden ACE(kininaz II) enzimini inhibe etmez. Dolayısıyla, bradikinine bağlı etkilerin artması ve ödem oluşması (losartan %1.7, plasebo %1.9) gibi AT1 reseptör blokajı ile direkt olarak bağlantılı olmayan olaylar losartan ile görülmez. Oral uygulama sonrası losartan iyi emilir ve ilk-geçiş metabolizması sonrası aktif bir karboksilik asit metaboliti ve diğer inaktif metabolitleri oluşur.Losartan tabletlerinin sistemik biyoyararlanımı yaklaşık %33'tür. Losartan ve aktif metabolitinin ortalama zirve konsantrasyonuna ulaşma süreleri sırasıyla 1 ve 3-4 saattir. İlacın standardize bir yemek ile uygulanması sonrasında losartanın plazma konsantrasyon profilinde klinik açıdan önemli bir değişiklik rastlanmamıştır. Hem losartan, hem de aktif metaboliti %99 ve daha yüksek bir oranda, öncelikle albümin olmak üzere, plazma proteinlerine bağlanır. Losartanın dağılım hacmi 34 litredir. Fareler üzerinde yapılan çalışmalar losartanın kan-beyin bariyerini çok zayıf olarak geçtiğini göstermektedir. Losartan ve aktif metabolitinin plazma klirensi sırasıyla 600mL/dak. ve 50 mL/dak.'dır. Losartan ve aktif metabolitinin renal klirensi ise sırasıyla 74 mL/dak. ve 26 mL/dak.'dır. Losartanın oral uygulaması sonrası dozun yaklaşık %4'ünün değişmeden, %6'sının ise aktif metabolit halinde idrar yoluyla atıldığı belirlenmiştir. 8 hafta boyunca tedavi edilen proteinürili (≥ 2g/24 saat) nondiyabetik hipertansif hastalara uygulanan 50 mg'dan 100 mg'a kitre edilen losartan potasyum, proteinüri miktarını %42 gibi önemli bir oranda düşürmüştür. IgG ve albüminin fraksiyonel itrahı da anlamlı olarak azalmıştır. Bu hastalarda losartan glomeküler filtrasyon hızını korumuş ve filtrasyon fraksiyonunu azaltmıştır. Losartanın otonom refleksler üzerinde ve plazma noradrenalini üzerinde uzamış bir etkisi yoktur. Sol ventrikül yetmezliği olan (New York Heart Association Fonksiyonel Sınıflar II-IV) ve çoğu diüretik ve/veya digital ile tedavi gören hastalarda yapılan 12 haftalık bir paralel çalışmada günlük 2.5, 10, 25, 50 mg şeklinde dozlarda uygulanan losartan potasyum, plasebo ile karşılaştırılmıştır. 25 ve 50 mg'lık dozlar tüm çalışma boyu süresi pozitif hemodinamik ve nöhormonal etki göstermiştir. Hemodinamik yanıtlar; kardiyak indekste artış ve pulmoner kapiler kama basıncında, sistemik vasküler dirençte, ortalama sistemik arteryel basınçta ve kalp hızında düşme ile karakterizedir. Bu kalp yetmezliği hastalarında hipotansiyon oluşumu doza bağlı olmuştur. Nörohormonal sonuçlar ise dolaşımdaki aldosteron ve noradrenalin düzeylerinde düşüş şeklinde görülmüştür. **ENDİKASYONLAR:** COZAAR hipertansiyon tedavisinde endikedir. Tek başına ya da diğer antihipertansif ajanlarla birlikte kullanılabilir. **KONTRENDİKASYONLAR:** COZAAR, ürünün içinde bulunan herhangi bir maddeye aşırı duyarlılık gösteren hastalarda kontrendikedir. **UYARILAR/ÖNLEMLER:** İntravasküler hacim azalması olan hastalarda (örneğin yüksek doz diüretikler ile tedavi edilmiş olanlar) semptomatik hipotansiyon oluşabilir. Bu şartlar COZAAR ile tedaviye başlanmadan önce düzeltilmeli veya daha düşük bir başlangıç dozu uygulanmalıdır (bkz. DOZAJ VE UYGULAMA). Farmakokinetik veriler, sirozlu hastalarda plazma losartan konsantrasyonunun önemli derecede arttığını göstердiği için hepatik bozukluk öyküsü olan hastalarda daha düşük bir doz göz önüne alınmalıdır (bkz. DOZAJ VE UYGULAMA ve FARMAKOLOJİK ÖZELLİKLER). İki taraflı renal arter stenozu veya tek renal arter stenozu olan hastalarda renin angiotensin sistemini etkileyen diğer ilaçlar kan üre ve serum kreatinin düzeyini yükseltebilirler. Tamamiyle kesinlik kazanılmamış olmasına rağmen bu durum angiotensin II reseptör antagonistleriyle de ortaya çıkabilir. **Gebelik:** Renin angiotensin sistemi üzerinde etkili olan ilaçlar, gebeliğin ikinci ve üçüncü trimesterinde kullanıldığında, oligmakta olan fetusta hasara hatta ölüme yol açabilir. Gebelik durumu söz konusu olduğunda COZAAR kullanımına en kısa zamanda son verilmelidir. Gebe kadınlarda COZAAR kullanımı üzerine herhangi bir çalışma olmadığı halde hayvanlar üzerinde losartan potasyum ile yapılan çalışmalar farmakolojik yolla renin angiotensin sistemine yapılan etkinin letal ve neonatal hasara ve ölüme yol açtığını göstermektedir. İnsanlarda renin angiotensin sisteminin oluşmasına bağlı fetal renal perfüzyon, gebeliğin ikinci üç aylık döneminde başlamaktadır. Bu yüzden fetus riskleri COZAAR'ın gebeliğin ikinci ve üçüncü üç aylık döneminde uygulanması ile artmaktadır. **Emziren Anneler:** Losartanın anne sütüne geçip geçmediği bilinmemektedir. Birçok ilacın anne sütüne geçtiği ve bunun emzirilen bebekte yaratığı istenmeyen etkiler göz önüne alınarak ilacın anne için önemi saptandıktan sonra emzirmeye veya ilaç kullanımına son verilmesi hakkında bir karara varılmalıdır. **Çocuklarda Kullanım:** Çocuklarda güvenliliği ve etkinliği henüz kanıtlanmamıştır. **Yaşlılarda Kullanım:** Klinik araştırmalarda losartanın güvenilirlik ve etkinlik profillerinde yaşa bağlı farklılıklara rastlanmamıştır. **YAN ETKİLER / ADVERS ETKİLER:** COZAAR genel olarak iyi tolere edilir. Yan etkileri hafif ve geçici olup tedavinin kesilmesini gerektirmez. COZAAR ile bildirilen toplam yan etki insidansı plasebo ile karşılaştırılabilir düzeydedir. Esansiyel hipertansiyonda yapılan kontrollü klinik çalışmalarda COZAAR ile tedavi edilen hastaların %1 veya daha fazlasında plaseboya oranla daha fazla görülen ilaca bağlı tek yan etki baş dönmesi olarak saptanmıştır. Buna ilaveten hastaların %1'inden daha azında doza bağlı ortostatik etkiler görülmüştür. Kontrollü klinik çalışmalarda insidansı plasebonunkinden az da olsa nadiren döküntü görülmüştür. **Laboratuvar Test Bulguları:** Kontrollü klinik çalışmalarda COZAAR uygulaması ile standart laboratuvar parametrelerinde önemli bir klinik değişime gözlenmemiştir. Hastaların %1.5'inde hiperkalemi (serum potasyumu > 5.5 mEq/L) saptanmış ama losartan tedavisinin kesilmesi gerekli görülmemiştir. ALT değerlerinde yükselmelere nadiren rastlanmış ve tedavinin kesilmesi ile tekrar normale dönmüştür. **BEKLENMEYEN BİR ETKİ GÖRÜLDÜĞÜNDE DOKTORUNUZA BAŞVURUNUZ. İLAÇ ETKİLEŞİMLERİ:** Klinik önem taşıyan hiçbir ilaç etkileşimine rastlanmamıştır. Klinik farmakokinetik araştırmalarda hidroklorotiazid, digoksin, warfarin, simetidin ve fenobarbital ile çalışmalar yapılmıştır. **DOZAJ VE UYGULAMA:** Birçok hasta için başlangıç ve idame dozu günde bir defa 50 mg'dır. Azami antihipertansif etki, tedavinin başlangıcından 3 ile 6 hafta sonra elde edilir. Bazı hastalar, doz günde bir defa 100 mg'a yükseltildiğinde ek bir fayda görebilirler. İntravasküler hacim azalması olan hastalarda (örneğin yüksek doz diüretik tedavisi görenler) başlangıç dozu olarak günde bir defa 25 mg dozu önerilmektedir (bkz. UYARILAR / ÖNLEMLER). Yaşlı hastalar veya diyaliz dahil olmak üzere renal bozukluğu olan hastalarda, başlangıç doz ayarlaması gerekli değildir. Hepatik bozukluk öyküsü olan hastalarda daha düşük doz uygulamaları düşünülmelidir (bkz. UYARILAR / ÖNLEMLER). COZAAR diğer antihipertansif ajanlarla birlikte kullanılabilir. COZAAR aç karnına veya tok karnına kullanılabilir. **DOZ AŞIMI:** İnsanlarda doz aşımı ile ilgili veriler sınırlıdır. Hipotansiyon ve taşikardi aşırı dozun yol açabileceği en önemli reaksiyonlar olup parasempatik (vagal) stimulasyon sonucunda bradikardi de görülebilir. Semptomatik hipotansiyon durumunda destekleyici tedavi gerekir. Losartan ve aktif metaboliti hemodiyaliz ile uzaklaştırılamazlar. **SAKLAMA KOŞULLARI:** 30°C'in altında, kuru bir yerde ve ışıktan koruyarak muhafaza ediniz. **İKAZLAR:** Hekime danışılmadan kullanılmamalıdır. Çocukların ulaşamayacağı yerde ve ambalajında saklayınız. **TİCARİ TAKDİM ŞEKLİ VE AMBALAJ MUHTEVASI:** 28 film tablet'lik blister ambalajlarda.Reçete ile satılır. Ruhsat Tarihi: 02/05/1996 Ruhsat No: 178/12

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