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ADRENAL INCIDENTALOMA CASES: CLINICAL, LABORATORY AND IMAGING CHARACTERISTICS OF 62 PATIENTS

Rıfat Emral* ✣ Vedia Tonyukuk* ✣ Defne Önür* ✣ Demet Çorapçıoğlu*
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SUMMARY

In this study, we reviewed the records of patients who were referred to our endocrinology and metabolic diseases department between the years 1992 and 2000, because of adrenal incidentalomas. There were a total of 62 patients (female/male: 3.43) between the ages of 23 and 73 years (median: 46.25 years). All were being evaluated for problems unrelated to adrenals at the time of diagnosis. Adrenal tumors were detected by either abdominal ultrasonography (39 cases, 62.9%), abdominal CT (18 cases, 29.0%), or thoracic CT (5 cases 8.0%). All were subsequently evaluated by surrenal CT and 17 (27.4%) were also evaluated by MRI. Adrenal masses were unilateral in 60 patients (right/left:1.31). The sizes ranged between 1 and 18 cm (mean 3.84cm). Twenty eight of them (45.1%) were larger than 4 cm in diameter. Of the patients with incidentalomas, 36 (58.0%) patients had concomitant hypertension, 28 (45.1%) had type 2 diabetes mellitus and 23 (37.0%) had a body mass index >25 kg/m^2.

Six (9.6%) cases were diagnosed as subclinical Cushing's syndrome. The diagnosis was made by at least two abnormal test results evaluating pituitary - adrenal function. Most common abnormality was the lack of dexamethasone suppressibility. Two (3.2%) patients were diagnosed as primary hyperaldosteronism. Of the 9 that were operated for malignancy 5 (55.6%) were pathologically evaluated as adrenocortical carcinomas. A total of 32 patients were operated. The pathology reports were as follows: Adrenocortical adenoma (9; 28.1%), adrenal nodular hyperplasia (4; 12.5%), adrenocortical carcinoma (5; 15.6%), pheochromocytoma (2; 6.3%), myelolipoma (6; 18.8%), adrenal cyst (2; 6.3%), lymphangioma (1; 3.1%), hemangioma (1; 3.1%) and non-tumoral formation (2; 6.3%). The size of carcinomas ranged from 5 to 18 cm, while the size of nonmalignant tumors ranged from 1 to 8.3 cm.

In conclusion all adrenal incidentalomas should be evaluated for malignancy and subclinical hormone production. It is prudent to operate cases with hormone overproduction, masses >4 cm and masses with radiological stigmata of malignancy. Others should be followed for subsequent changes in hormone production or size.

Key Words: *Adrenal Gland, Incidentaloma, Subclinical Cushing's Syndrome.*

ÖZET

Adrenal İnsidentalomalı Vakalar: 62 Hastanın Klinik, Laboratuvar ve Görüntüleme Özellikleri

Bu çalışmada, 1992 ve 2000 yılları arasında hastanemiz endokrinoloji ve metabolizma hastalıklar bölümüne adrenal insidentaloma nedeni ile başvuran hastaların kayıtları incelendi. Yaşları 23 ile 73 arasında değişen (ortalama: 46.25 yıl) toplam 62 hasta (kadın/erkek:3.43) çalışmaya alındı. Tanı anında tüm hastalar adrenal bezlerle ilgili olmayan hastalıklar nedeni ile incelenmekteydiler. Adrenal tümörler ultrason (39 olgu, %62.9), abdominal tomografi (18 olgu, %29.0), ya da toraks tomografisi (5 olgu, %8.0) ile tespit edilmişti. Hepsi sürrenal tomografi ile yeniden değerlendirilmişti. 17 olgu (%27.4) ayrıca MRG ile de değerlendirilmişti. Adrenal kitleler 60 hastada (sağ/sol: 1.31) tek taraflıydı. Boyları 1 ile 18 cm arasında değişmekteydi (ortalama: 3.84 cm). Kitlelerin 28'i (%45.1) 4 cm'den büyüktü. İnsidentalomalı hastalardan, 36'sında (%58.0) eşlik eden hipertansiyon, 28'inde (%45.1) tip 2 diabetes mellitus vardı ve 23'ünde (%37.0) vücut kitle indeksi >25 kg/m^2 idi.

Olguların 6'sında (%9.6) subklinik Cushing sendromu tespit edilmişti. Tanı pitüiter – adrenal aksı değerlendiren en az iki test sonucunun bozulmuş olması ile konulmuştu. Saptanan en sık bozukluk deksametazon testi ile baskılanma olmamasıydı. İki (%3.2) hastada hiperaldosteronism saptanmıştı. Malignite şüphesi ile ameliyat olan 9 hastadan 5'inin (%55.6) patoloji raporu adrenokortikal karsinom olarak bildirilmişti. Toplam 32 hasta ameliyat edilmişti. Patoloji raporları 9 hastada (%28.1) adrenokortikal adenom, 4 hastada (%12.5) adrenal nodüler hiperplazi, 5 hastada (%15.6) adrenokortikal karsinom, 2 hastada (%63.) feokromositoma, 6 hastada (%18.8) miyelolipom, 2 hastada (%6.3) adrenal kist, 1 hastada (%3.1) lenfanjiom, 1 hastada (%3.1) hemanjiom ve 2 hastada (%6.3) tümöral olmayan oluşumlar olarak bildirilmişti. Karsinomların boyları 5 ile 18 cm, malign olmayan kitlelerin boyları ise 1 ile 8.3 cm arasında değişmekteydi.

Sonuç olarak tüm adrenal kitleler malignite ve subklinik hormon üretimi açısından değerlendirilmelidir. Hormon üretimi olan, boyu >4cm olan ve radyolojik olarak malignite düşündüren kitlelerin ameliyat edilmesi düşünülmelidir. Diğerleri hormon üretiminde ya da boyutlarda değişiklik olması açısından takib edilmelidir.

Anahtar Kelimeler: *Adrenal Bez, İnsidentaloma, Subklinik Cushing Sendromu*

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Adrenal incidentalomas are adrenal masses larger than 1 cm, detected during a non-invasive imaging study for a non-adrenal complaint. In a study by Barzon et al, the most common reasons for the imaging study were found to be nonspecific abdominal pain (29%), follow-up investigations for several diseases (%12), and hepatocholecystopathy (12%), followed by postoperative follow-up (11%), lumbar pain (%7), nephropathy (5%)... etc (1). However, when re-evaluated retrospectively, many patients were found to have symptoms and signs of an adrenal pathology. The definition of adrenal incidentaloma, covers a wide clinical spectrum: adrenocortical and medullary tumors, benign or malign lesions, hormonally active and inactive lesions, metastasis, infections or granulomatous lesions (1-5).

During the recent years, with frequent employment of higher resolution, non-invasive imaging techniques, the problem of detection of previously unnoticed masses have risen. Prevalence has been reported to be 0.35–4.4 % with computed tomography, while it is 1.4–5.7 % in autopsy series (2). Published data report that about 10 % of the cases are bilateral (5). Bilateral incidentalomas should arise the possibility of a metastatic disease, congenital adrenal hyperplasia, lymphoma, infection (tuberculosis, fungi), hemorrhage, ACTH dependent Cushing's syndrome, pheochromocytoma, amyloidosis and infiltrating diseases of the adrenals (6).

Incidentally discovered adrenal masses are fairly common, however there are some controversies concerning the interpretation of hormonal studies and the methods of management. Although the majority of masses are non-secretory adrenocortical adenomas, some may be a primary or a metastatic malignancy of the adrenals, or may have minor undetected endocrine findings or subclinical hypersecretory function. Management of adrenal masses is aimed at differentiating malign from benign masses, and functional adenomas from nonfunctional masses (1). For this, imaging characteristics of the masses and hormonal panels are utilized.

In this study we summarize the clinical, laboratory and imaging characteristics of a group of Turkish patients that were evaluated for incidentally detected adrenal masses. Results of pathology studies are included where possible.

Patients and Methods

We reviewed the hospital records of patients who were referred to the Department of Endocrinology and Metabolic Diseases of Ankara University, School of Medicine, Ibn-i Sina Hospital (Ankara, Turkey) between the years of 1992 and 2000, because of adrenal tumors incidentally found during radiological imaging for non-adrenal complaints.

Hospital records were retrospectively examined for clinical, laboratory and radiological evaluation of patients. In addition to a routine systemic oncological screening results, endocrine tests evaluating pituitary - adrenal function (basal plasma concentrations of ACTH, cortisol, urinary free cortisol levels, 1 mg, 2 mg, and 8 mg dexamethasone suppression tests), serum potassium concentrations, 24 hour urinary VMA and metanephrine values; ultrasound, CT and MRI results; pathology reports of operated cases were recorded.

Normal circadian rhythm was defined when the cortisol levels decreased by 50% in the evening. One mg and 2 mg dexamethasone suppression tests were performed as overnight tests. Morning plasma cortisol levels <5 mg/dl as a response were accepted as normal. Eight mg dexamethasone suppression test was performed by administration of 2 mg dexamethasone every 6 hours for two days and collection of 24-hour urine sample on the second day. A decrease in the urinary free cortisol level to more than 50 % of the basal value, was accepted as normal. This test was performed only when there was a clinical suspicion of Cushing's syndrome.

Surgery was performed when the mass was found to be hormonally active, was over 3–4 cm in diameter, clinical suspicion of a malignancy was high or, in one case, an operation for cholecystectomy was being planned.

There were a total of 62 patients (female/male ratio: 3.43) between the ages of 23 and 73 years (median: 46.25). All patients were being evaluated for problems unrelated to adrenal glands at the time of diagnosis. Of them, 17 (27.4%) were being evaluated for gastrointestinal complaints, 11 (17.7 %) for nonspecific lumbar pain, 9 (14.5 %) for respiratory problems, 8 (12.9 %) for newly diagnosed mild hypertension - excluding cases with hypokalemia-, 5 (8.0 %) for urological complaints, 12 (19.3 %) for other reasons.

The gastrointestinal symptoms and signs that prompted an investigation were abdominal pain, cholelithiasis, spastic colon, dyspepsia, dysphagia, abdominal bloating, hematochesia. Respiratory symptoms and signs that prompted an imaging study were chest pain, dyspnea, pleurisy, cough, and right lower lobe atelectasis on chest X-ray. Urolithiasis, renal colic, polyuria were the urological complaints prompting an imaging study. Other patients were being evaluated for an elevated erythrocyte sedimentation rate, gluteal abscess, multiple myeloma, pregnancy, rheumatoid arthritis, hermaphroditism, iron deficiency anemia, Meniere's disease, abdominal cramps, hoarseness or irregular menses (none had typical symptoms or signs of adrenal pathology).

Adrenal tumors were detected by either abdominal ultrasonography (39 cases, 62.9%), abdominal computed tomography (CT) (18 cases, 29.0%), or thoracic CT (5 cases, 8.0%). All lesions were subsequently evaluated by a surrogate CT and 17 cases (27.4%) were also evaluated by magnetic resonance imaging (MRI).

Results

Adrenal masses were unilateral in 60 patients (96.8%). Right to left ratio was found to be 1.31. The size of masses ranged between 1cm and 18 cm (mean 3.84). Records revealed that 36 (58.0%) patients had concomitant hypertension, 28 patients (45.1%) had diabetes and 23 patients (37.0%) were obese (had a body mass index > 25 kg/m^2). Of the adrenal masses, 28 (45.1%) were larger than 4 cm.

Six cases (10.0%) were diagnosed as subclinical Cushing's syndrome (Records of one patient were unavailable). The diagnosis of subclinical Cushing's syndrome was made by at least two abnormal test results evaluating pituitary - adrenal function. Most common abnormality was the lack of dexamethasone suppressibility with 1 mg or 2 mg overnight dexamethasone testing (100%). Diurnal variation was absent in three patients. Early morning cortisol level was higher than normal in one patient.

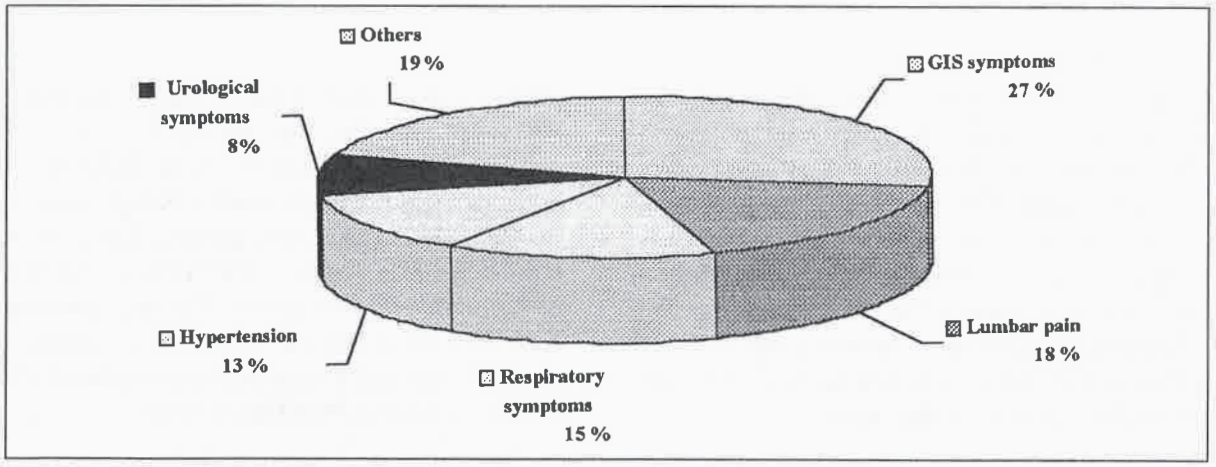

Figure 1: Presenting symptoms and signs of our patients with adrenal incidentaloma

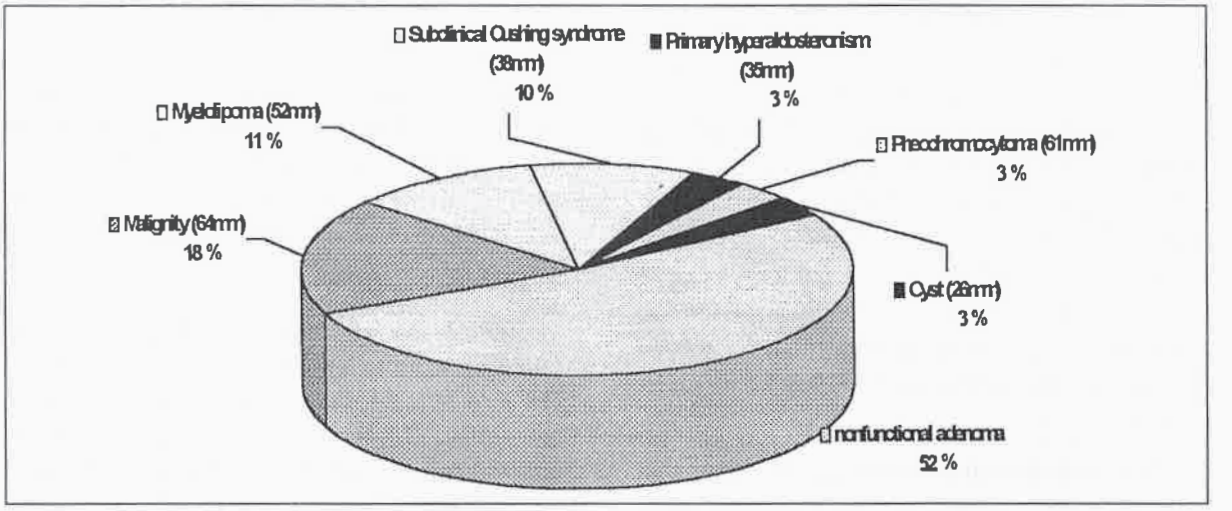

Figure 2: Clinical diagnosis of our patients (numbers in parenthesis denote mean sizes)

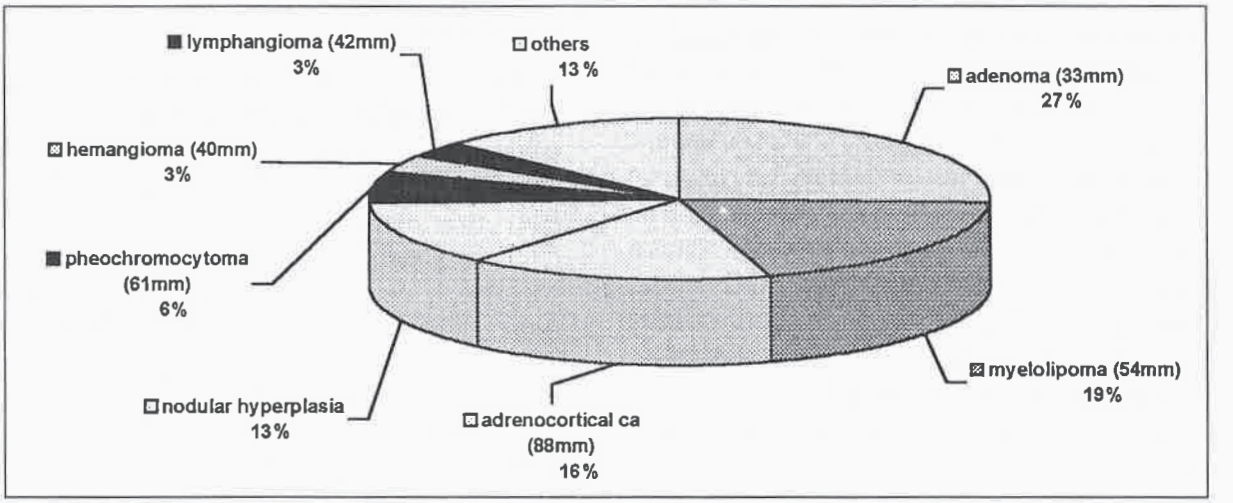

Figure 3: Histopathological diagnosis of patients who underwent operation (numbers in parenthesis denote mean sizes)

Two cases (3 %) were diagnosed as pheochromocytoma. Urinary catecholamine excretion was increased only in 1 patient. He was operated and the pathology report was pheochromocytoma. The other case was diagnosed as pheochromocytoma after surgical excision. This patient was an example for the silent or subclinical pheochromocytoma because of the lack of clinical and laboratory signs for the usual pheochromocytoma cases.

Two cases (3 %) were diagnosed as primary hyperaldosteronism. One was a 38-year-old women with a mass detected during pregnancy follow-up visits. She had hypertension that was regulated with doxazosin 2 mg bid. Serum potassium levels were 3.8 and 4.1mEq/l . Ratio of standing plasma concentration of aldosterone to plasma renin activity (PCA/PRA) was 47.2 and 61.17 on different occasions. The other case was a 46 year-old women who was found to have a mass during regular check-up examinations. She also had a ratio of PCA/PRA over 50.

Eleven cases (18 %) were clinically evaluated as malignancy. Of the nine that were operated, 5

(56 %) were pathologically evaluated as adrenocortical carcinomas. The others were reported to be an inflammatory mass, lymphangioma, necrotic material with foci of calcification, and nodular adrenal hyperplasia. Of the eleven patients one refused the operation, and the other could not be operated because of comorbidities.

A total of 32 patients were operated. The pathological findings were adrenocortical adenoma (9 cases, 28.1 %), adrenal nodular hyperplasia (4 cases, 12.5%), adrenal carcinoma (5 cases, 15.6%), pheochromocytoma (2 cases, 6.3 %), myelolipoma (6 cases, 18.8 %), adrenal cyst (2 cases, 6.3 %), lymphangioma (1 case, 3.1 %), hemangioma (1 case, 3.1 %) and non-tumoral formations (2 cases, 6.3 %). Of the incidentalomas that were operated, the size of carcinomas ranged from 5 to 18 cm (mean 8.8 cm), while the size of nonmalignant tumors ranged from 1.5 to 8.3 cm (mean 4.2 cm).

Discussion

Adrenal incidentalomas have become a great concern recently, since the advent of newer imaging modalities can detect clinically insignificant masses even more frequently. This study was one of the largest series in Turkey evaluating adrenal incidentalomas. There was a total of 62 cases, of which 2 presented with bilateral masses.

More than half of the cases were older than 50 years. Some studies have reported that incidence of nodules increased with age (7). Compensatory response to local ischemia and atrophy due to vascular changes with age, was the suggested pathogenic mechanism for this (8). As well, more imaging studies required from elderly patients compared to young, increased the chance of detection of a silent adrenal mass (5).

The finding that more women were detected with incidentalomas was also reported in an Italian series, and it was explained by the fact that, abdominal investigations are more frequently obtained for women than men because of more common hepatobiliary and pelvic disease, as the autopsy series revealed comparable frequencies of incidentalomas in men (8).

Most incidentalomas were detected by ultrasonography. This was explained by the fact that, it is the choice of study for many abdominal pathologies as it is easy to perform and cheaper. In our patients the incidentalomas tended to be on the right side (54.8 %). In the Italian series of adrenal incidentalomas, masses in the right adrenal were also more common. This finding was related to better visualization of the right adrenal gland by ultrasonography, which was the most commonly utilized imaging modality (5, 8).

Reported data reveal that while 67–94 % of adrenal incidentalomas are silent, non-functioning adenomas, a considerable number of incidentalomas may show hormonal activity without any clinical symptoms or signs (5). Endocrine abnormalities have been reported in many adrenal incidentaloma cases (1). This is important to bear in mind during clinical practice, as hormone excess syndromes (hypercortisolism, aldosteronism, pheochromocytoma) cause significant morbidity (1). Therefore first step in evaluating an adrenal mass is to determine if it bears hormonal activity or not.

Most patients with adrenal incidentalomas may have slight excess of cortisol secretion that may only slightly affect one of the tests, and not have clinical signs of hypercortisolism. Subclinical Cushing's syndrome is diagnosed in patients with no signs of Cushing's syndrome but laboratory evidence of hypercortisolism affecting two or more laboratory tests (1,8). Daily cortisol production is within normal limits, but diurnal variation is lost and plasma levels of cortisol cannot be suppressed by dexamethasone (9). In different series, adrenal incidentaloma cases with a diagnosis of subclinical Cushing's syndrome were reported to have decreased basal ACTH in 5–34 %, loss of diurnal rhythm in 8–20 %, increased urinary free cortisol in 0–21 %, increased plasma cortisol level in 0–12 % (3,4). Some have reported that decreased levels of DHEA-S were due to suppression by increased levels of cortisol, and therefore related to a

benign tumoral mass, however this finding was not confirmed by other studies (1). Dynamic studies of the pituitary-adrenal axis includes dexamethasone suppressibility tests. One mg dexamethasone test is reported to have a high incidence of false positive results (1). With this test, lack of suppression is observed in 12–20 % of patients with adrenal incidentalomas (3,4). Therefore it is recommended as a screening test. When the patients are found to be positive, high dose dexamethasone suppression tests should be performed (1, 10). Some authors recommend repeat testing with 1 mg dexamethasone during follow-up, if initially negative.

Subclinical Cushing's syndrome was diagnosed in six of our patients. In concordance with the published data, it was the most common endocrine abnormality in our patients with incidentalomas. Diagnosis of subclinical Cushing's syndrome was made on the basis of two abnormal laboratory test results concerning the pituitary–adrenal axis. Most common abnormality detected was the lack of dexamethasone suppressibility.

Although typical hypercortisolism findings are not present, patients with subclinical Cushing's syndrome are frequently reported to have a higher incidence of hypertension, diabetes mellitus, obesity, and altered bone metabolism (1, 6, 9, 11). Diabetes mellitus, hypertension and obesity are common problems in the elderly population in Turkey. Hypertension is commonly accepted as essential unless it has an abrupt; early or late onset. Many cases of diabetes are under-diagnosed, and obesity is only recently being recognized as a metabolic disease. Therefore, many cases of subclinical Cushing's syndrome probably pass undetected, unless an imaging study for another reason is performed. In our series of patients, more patients with subclinical Cushing's syndrome had either hypertension or diabetes mellitus compared to patients with non-secretory adenomas or carcinomas. This could be due to slightly higher levels of cortisol as well as a higher mean age of the patient population (median age: 60.6 years).

In the light of the present data, whether progression to overt Cushing's syndrome is common in those patients is unclear (10, 12). In the study of Terzolo et al, spontaneous normalization of cortisol levels in 50 % of patients and no progression to overt Cushing's syndrome have been reported (10). However in another study the hormonal abnormalities have either remained unchanged, or have progressed into clinically overt syndromes (12). In some series enlargement of the mass and/or increment in hormone excess are reported during follow-up, 0–11% and 0–16% respectively (4, 10, 12).

There are reports that unilateral adrenalectomy improves arterial blood pressure, glycemic regulation and weight loss in patients with subclinical Cushing's syndrome (1, 6, 9, 11). Some authors therefore, recommend surgical excision for patients with subclinical hypercortisolism, if poor control of hypertension, diabetes, osteoporosis are present (11,13). Screening incidentaloma patients for subclinical Cushing's syndrome preoperatively is also important because of the increased risk of adrenal insufficiency postoperatively (14).

Pheochromocytoma was diagnosed in two patients. Both were being investigated for lumbar pain. They were both operated and the diagnosis confirmed pathologically. Pheochromocytoma are the second most common causes of incidentalomas (9). Autopsy series have revealed that about 76% of pheochromocytoma cases are clinically silent. About 1.5–11% of adrenal incidentalomas are pheochromocytomas (2,3,4,6). Pheochromocytomas may be difficult to distinguish from carcinomas by radiological methods, and exclusion of possibility of a pheochromocytoma preoperatively is mandatory to prevent fatal complications. Evaluation with 24-hour urinary catecholamine and VMA and metanephrine (catecholamine metabolites) excretion should be performed in each case. Performed together, those tests can diagnose 99% of the cases (1,6). Ito et al have reported that, spot tests for urinary catecholamine and metanephrine levels are also accurate, since secretion rates of metanephrine and normetanephrine are constant (15).

Primary hyperaldosteronism was diagnosed in two of our patients. Primary hyperaldosteronism is reported to be the most common cause of secondary hypertension in patients not consuming nicotine (6). However they comprise only 1.5–3.3% of adrenal incidentalomas (3). This is because of early recognition of the signs and symptoms of hyperaldosteronism, even before the mass can be detected (8, 14). It must be kept in mind that, contrary to the general belief, patients with hyperaldosteronism are frequently normokalemic, probably because of restriction of salt intake (1,6). Most specific test is reported to be the ratio of standing plasma concentration of aldosterone to plasma renin activity. Results higher than 20, or PCA higher than 15 ng/dL are considered to be positive (1, 6). A few patients may have normal levels, but lack suppression of aldosterone by fluodrocortisol (9).

Of the nine patients who were operated with the clinical suspicion of a malignancy five were confirmed pathologically to be adrenocortical carcinomas. Clinical suspicion of malignancy for an adrenal mass should arise if the mass shows certain features depending on the imaging study undertaken, or if the mass enlarges during the follow-up period (6). In our series, one patient was operated for an enlarging mass. Other patients had incidentalomas larger than 4 cm, with irregular borders, showed no loss of intensity on T2 sequences with MRI, or low attenuation (density higher than 18 Hounsfield units) on CT which were all in favor of a malignancy (16).

The size is a major determinant for management of incidentalomas since about 90% of adrenocortical carcinomas are larger than 6 cm (1,8). There is a consensus for surgical excision of masses larger than 6 cm (1). However for masses 2.5–5 cm there is still controversies. It is generally accepted that masses over 3–4 cm should be excised (2,4,8). The largest mass in our series was 180 mm and was a 35-year-old male who was diagnosed adrenal carcinoma. In our series, the sizes of carcinomas ranged from 5–18 cm, with a mean of 8.8 cm; while nonmalignant lesions ranged from 1 cm to 8.2 cm with a mean of 4.2 cm. Therefore a cut-off size of 4 cm is reasonable for mass excision, because of an increased risk of malignancy.

Plasma dehydroepiandrosterone (DHEA) is reported to be an efficient method for discriminating adrenal malignancies. However patient records that we evaluated, seldom included DHEA level. This was probably because of recent availability of the test in the laboratory and the diagnosis or exclusion of a malignancy by radiological examinations.

Age distribution showed a tendency towards an older age, 64.5% of patients were over 50 years. Patients with malignant lesions were younger (between 34–48 years, mean: 43.4), compared to patients with adenomas (40-73 years, mean: 60.6). This is in concordance with the previous reports (8). It is recommended that patients younger than 50 years should also be operated, since the risk of a carcinoma is higher (1).

Scintigraphic studies with 131 I-NP59 is reported to be important in discriminating patients with malignancies. Active lesions are considered to be benign lesions (6). Cold nodules are either primary or secondary malignancies or mass lesions causing tissue destruction (hemorrhage, cysts, myelolipomas) (17). It is the preferred method of evaluation in some centers, since they are cost-effective (17, 18). However it is ineffective in detecting masses smaller than 2 cm (1). It is not used as a routine examination in our center. However 131 I-MIBG scintigraphic studies for medullary masses are performed, when a diagnosis of pheochromocytoma is being considered.

Radiological findings were the most accurate for myelolipomas, which are benign masses of composed of adipose tissue and hemopoietic tissue. Therefore they can easily be differentiated radiologically from adenomas and carcinomas (1). Since progression or complication risk is negligible, asymptomatic cases can be followed without operation (1). Six patients were operated with the tentative diagnosis of a myelolipoma and the diagnosis was confirmed by pathology reports

in all of them. The criteria of operation for those cases was a mass larger than 4 cm. One case was a sickle cell anemia patient with a 5 cm myelolipoma detected on ultrasonographic examination during a crisis. He was operated for cholecytitis during the mass was subsequently resected.

In conclusion, evaluation of patients with incidentalomas is a team work of endocrinologists, radiologists, and surgeons. Many algorithms for management of adrenal incidentalomas have been proposed.

In our series of Turkish patients with adrenal incidentalomas, patients were evaluated for exclusion of a syndrome of hormone excess or an adrenocortical carcinoma. Subclinical hormone production were detected by laboratory tests while the possibility of a malignancy was evaluated by radiological methods, by CT or MRI. Cases with hormone overproduction, and masses with radiological stigmata of malignancy were operated. Other cases were kept in follow-up to detect subsequent changes in hormone production or size.

About half of the patients operated with the suspicion of malignancy were found to have benign lesions. In the feature improvement of imaging techniques or utilization of new serum markers of malignancy may improve the decision of operation for the tentative diagnosis of malignancy.

Meanwhile, a new study has been launched to determine the clinical significance of subclinical Cushing's syndrome in our patients, which will help us plan feature management guidelines for those patients.

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THE PREVALENCE OF LATE ONSET CONGENITAL ADRENAL HYPERPLASIA IN HIRSUTE WOMEN FROM CENTRAL ANATOLIA

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SUMMARY

Objective: *Late onset congenital adrenal hyperplasia (LO CAH) can be seen in association with polycystic ovary syndrome (PCOS) or idiopatic hirsutism (IH). The study aimed to find out the prevalence of LO CAH in Central Anatolia among hirsute women.*

Study Design: *Sixty-three patients with hirsutism were evaluated to determine the frequency of LO CAH by comparing with their age and body mass index matched 28 healthy controls. Of those 63 hirsute women, 31 were diagnosed as PCOS, and 32 were diagnosed as IH. Following basal hormonal evaluation, all subjects underwent ACTH stimulation test and ACTH stimulated 17-hyroxyprogesterone (17-OH P), 11-desoxycortisol (11-DOC), cortisol (F), and dehydroepiandrosterone sulfate (DHEA-S) levels were determined in all subjects.*

Results: *ACTH stimulated 17-OH P, 11-DOC, and DHEA-S levels did not differ between groups. However, stimulated F levels were found to be higher in hirsute women ($p<0.001$). Six out of 63 (9.52%) patients with hirsutism met the criteria for 21 hydroxylase deficiency. We found no subject presumed to have 11-β hydroxylase deficiency, but one subject in control group (3.57%) and two patients among PCOS subjects (6.45%) had exaggerated DHEA-S response which was suggestive for mild 3-β hydroxysteroid dehydrogenase deficiency.*

Conclusion: *The most frequent form of LO CAH seems to be due to 21 OH deficiency among women with PCOS and IH in Central Anatolia. Mild 3-β HSD deficiency may also be an underlying cause for hirsutism and it may be seen without any clinical presentation. Adrenal hyperactivity is the main reason of hyperandregenemia in women with hirsutism.*

Key Words: *ACTH, hirsutism, late onset congenital adrenal hyperplasia.*

ÖZET

Orta Anadolu Bölgesi'ndeki Hirsut Kadınlarda Geç Başlangıçlı Konjenital Adrenal Hiperplazi Sıklığı

Giriş: *Geç başlangıçlı konjenital adrenal hiperplazi, polikistik over sendromu (PKOS) ile ya da idiopatik hirsutizm (İH) ile birliktelik gösterebilir. Bu çalışmanın amacı Orta Anadolu Bölgesi'nde hirsutizmi olan kadınlar arasında geç başlangıçlı konjenital adrenal hiperplazinin sıklığını saptamaktır.*

Çalışma Planı: *Bu çalışmada hirsutizmli 63 kadın hasta yaş ve vücut kitle indeksi eşleştirilmiş 28 sağlıklı kontrolle karşılaştırılarak, geç başlangıçlı konjenital adrenal hiperplazi sıklığı incelendi. Bu 63 hirstizmli kadından 31'i PKOS, 32'si İH olarak tanı aldı. Bazal hormonal incelemeyi takiben, çalışmaya alınan tüm vakalara ACTH uyarı testi yapılarak ACTH uyarısı sonrası 17-hidroksiprogesteron (17-OH P), 11-dezoksikortizol (11-DOC), kortizol (F) ve dehidroepiandrosteron sülfat (DHEA-S) düzeyleri değerlendirildi.*

Sonuçlar: *ACTH uyarısı sonrası ölçülen 17-OH P, 11-DOC, ve DHEA-S değerlerinde gruplar arasında fark yoktu. Ancak uyarı sonrası F düzeyleri hirsüt kadınlarda daha yüksek olarak bulundu ($p<0,001$). 63 hastanın 6'sı (%9,52) 21 hidroksilaz eksikliği için kriterleri sağladı. 11-β hidroksilaz eksikliği olan olgu saptanmadı. Ama kontrol grubunda bir olguda ve PKOS'lu hastalardan ikisinde, hafif 3-β hidroksisteroid dehidrojenaz eksikliğini düşündürecek ACTH uyarısına abartılı DHEA-S yanıtı gözlendi.*

Yorum : *Orta Anadolu Bölgesi'nde PKOS ve İH'lı kadınlar arasında en sık görülen geç başlangıçlı konjenital adrenal hiperplazi formu 21 hidroksilaz eksikliğine bağlıdır. Ilımlı 3-β hidroksisteroid dehidrojenaz eksikliği de hirsutizm için bir neden olabilmektedir ve klinik belirti vermeyebilir. Hirsut kadınlarda hiperandrojenizm esas olarak adrenal hiperaktiviteye bağlıdır.*

Anahtar Kelimeler: *ACTH, hirsutizm, geç başlangıçlı konjenital adrenal hiperplazi,*

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Late-onset congenital adrenal hyperplasia (LO CAH) is a cause of a spectrum of clinical manifestations of postnatal androgen excess (1). However, because of the lack of the appropriate diagnostic test, women with the common complaints due to hyperandrogenemia, like hirsutism, oligoamenorrhea, acne etc. can easily be diagnosed as polycystic ovary syndrome (PCOS) or sometimes as idiopatic hirsutism (IH) when androgen levels are in normal ranges and if the woman has normal ovulatory cycles. Recent studies suggest that PCOS may develop in association with conditions with clearly defined adrenal androgen overproduction (2), like congenital adrenal hyperplasia (3). Polycystic ovaries have been shown frequently in patients with late onset 21 hydroxylase (21 OH) deficiency (3, 4), 11-β hydroxylase (11-β OH) deficiency (5), and 3-β hydroxysteroid dehydrogenase (3-β HSD) deficiency (6). All these forms of CAH have higher incidence in Middle East, among Jews and Arabs (7, 8).

The prevalence of LO CAH varies according to studied population. For example, Cobin et al and Benjamin et al reported the frequency of 21 OH deficiency in women with PCOS, 1% and 19% respectively (9, 10). Azziz et al found the prevalence of 11-β OH deficiency 0.8% in hyperandrogenism (11), but Şahin et al found its prevalence as high as 8.4% among 83 women with PCOS in Turkey (12). In an other study, Azziz et al pointed that 3-β HSD deficient LO CAH is also a rare condition in patients with hirsutism or hyperandrogenic oligomenorrhea (13). On the contrary, Solyom et al showed that 4/33 (12.12%) of adolescent girls with hirsutism had decreased 3-β HSD activity (14). Beside this, Meer et al found the prevalence of 3-β HSD deficiency 12.5% among 32 women with clinical manifestations of hyperandrogenism (15).

These different results also reflect the different diagnostic criterias used for LO CAH. There is no doubt that the main diagnostic evaluation should be based on molecular studies (16, 17), but this may limit to find out some cases since molecular studies are not prevalent and easy to do. On the other hand, there is still an enigma about the diagnosis of LO CAH by using hormonal analysis. Yet, ACTH stimulation test still consists of the gold standart test for the evaluation of adrenal response and enzyme deficiencies causing LO CAH (18, 19).

From this point of view, we evaluated our 63 patients with hirsutism to determine the frequency of LO CAH by comparing with their age and body mass index (BMI) matched 28 healthy control subjects.

Subjects and Methods

The study protocol was approved by the Ethical Committee of Ankara University, School of Medicine, and all the women gave informed consent. Ninety one women were enrolled into the study. Of those 91 women, 31 were diagnosed as PCOS and 32 were diagnosed as IH. The rest 28 women consisted of our control subjects (CS) and they were all eumenorrheic (intermenstrual interval between 21 and 35 days) and free of signs or symptoms of hyperandrogenemia. Hirsutism was evaluated by the modified Ferriman-Gallwey-Lorenzo index in nine body areas (20) by the same clinician. Only the women with a total score of 8 or more were accepted as hirsute. The diagnosis of PCOS was made by the presence of three or more of the following criterias: oligo/amenorrhea, hyperandrogenemia, hirsutism, the presence of polycystic ovaries on pelvic ultrasound examination, and a serum luteinizing hormone (LH): follicle stimulating hormone (FSH) ratio >2. Oligomenorrhea was defined as menstrual cycles >35 days in length and amenorrhea was defined as absent of menstrual period in more than six months. Without the presence of menstrual disturbances and any other signs or symptoms of hyperandrogenemia except hirsutism in the patient population, the diagnosis of IH was made.

The subjects in the study groups and controls were age and BMI matched. The mean ages and age ranges of women in PCOS, IH and CS groups were as follows: 24.71±3.92 years (17-34), 22.19±3.71 years (17-30), and 23.18±4.50 years (16-30), respectively. None of the subjects in any group had received any hormonal medication at

least eight weeks before the study. All the subjects were studied in the follicular phase (days 3-8) and in the event that the patient was amenorrheic, random a day.

Basal blood samples were obtained between 08.00 and 09.00 hours a.m. The following hormones were measured: LH, FSH, total testosterone (tT), free testosterone (fT), progesterone (P), estradiol (E_2), dehydroepiandrosterone sulfate (DHEA-S), cortisol (F), ACTH, prolactin (PRL), 17-hydroxyprogesterone (17-OH P) and 11-desoxycortisol (11-DOC). Basal androstenedione (A) and dihydrotestosterone (DHT) levels were also measured in patients with PCOS and IH.

ACTH stimulation test was performed in all subjects by administration of a single i.m. 1 mg synthetic ACTH-(1-24) (Synacthen amp, Ciba, Basel, Switzerland) in the fasting state in the supine position. Venous blood was withdrawn through an indwelling catheter at 0, 6 and 8 hours for determination of serum 17-OH P, 11-DOC, F and DHEA-S. After testing, the serum was separated and stored at $-20^{o}C$ until assayed. 17-OH P, 11-DOC, tT, fT, P, E_2, F, PRL, DHEA-S, and A were measured by direct radioimmunoassay, and DHT was measured by ELISA, using available kits.

The intra-assay coefficient of variations (CVs) for the measurement of A were 5.6%, 4.3%, and 2.8% for low, medium, and high levels, respectively. The inter-assay CVs for A were 9.8%, 6.0%, and 7.0% for low, medium, and high levels, respectively as well. For DHT intra-assay CVs were 11.4%, and 5.9%; inter-assay CVs were 12.1%, and 7.5%. The intra-assay CVs for the measurement of 17-OH P were 12.3%, 7.8%, and 8.3%; inter-assay CVs were 12.9%, 9.8%, and 12.8%, for low, medium, and high levels, respectively. For 11-DOC intra-assay CVs were 2.1%, 5.9%, and 4.3% and inter-assay CVs were 13.7%, and 11.6%. Intra-assay CVs of cortisol were between 3.2% and 2.2%, and inter-assay CV was 20%. For the measurement of DHEA-S, intra-assay CVs for low, medium, and high levels were as follows: 2.8%, 2.4%, and 1.7%, respectively.

ACTH stimulated 17-OH P levels >13.4 ng/ml were considered as the criteria of 21 OH deficiency. This cut-off was the value for the 95th percentile of our controls. On the other hand, the diagnosis of 11-β OH deficiency was made if the adrenal 11-DOC response to ACTH stimulation exceeded threefold the 95th percentile of controls (12, 21). Because of the technical impossibilities, we could not manage to measure 17-hydroxypregnenolone levels. So, determination of our patients for 3-β HSD deficient LO CAH was almost uncertain. Nevertheless, basal A levels and DHEA-S responses after ACTH stimulation were appreciated for the possible mild 3-β HSD deficiency. DHEA-S increase greater than 2 standard deviation (SD) above the mean of normal controls was taken as a prominent response to ACTH stimulation and accepted as the possible mild 3-β HSD deficiency (7, 22).

For statistical analyses One way ANOVA was used for the comparison of values in three groups. Comparison of 17-OH P levels in patients with and without 21 OH deficiency, and in healthy controls was made by the same method, and p value of <0.05 was regarded as statistically significant.

Results

Basal hormone levels in three groups are seen at Table 1.

Hirsutism scores were found to be 11.29±3.96 in PCOS patients and 9.31±5.05 in IH patients; the difference was not significantly different. About 2/3 of the patients with PCOS had oligoamenorrhea (64.5%). The family history for hirsutism was found in 11/31 (35.5%) of patients in PCOS group and in 9/32 (28.1%) of patients in IH group.

As would be expected LH/FSH ratio was significantly higher in PCOS group comparing with IH and CS groups (1.78±1.57 vs 0.78±0.44 and 0.93±0.59; $p<0.01$ and $p<0.01$, respectively). There was a parallelism between basal LH, FSH levels and LH/FSH ratios. Basal LH levels were higher in patients with PCOS than in patients with IH ($p<0.001$). In contrast, control

Table 1: Comparison of the basal hormone levels in three groups (mean ± SD)

		Polycystic ovary syndrome (n: 31)	Idiopatic hirsutism (n: 32)	Control subjects (n: 28)	p*
LH	(IU/ml)	9.50±1.65	3.87±0.33	6.19±0.67	<0.001[a]
FSH	(IU/ml)	5.38±0.36	5.43±0.35	8.02±1.35	<0.05[b]
LH/FSH		1.78±1.57	0.78±0.44	0.93±0.59	<0.01[c]
E_2	(pg/ml)	80.75±48.21	67.98±38.20	49.52±28.48	<0.05[d]
P	(ng/ml)	1.49±2.70	1.57±3.20	1.21±1.60	NS
tT	(ng/ml)	65.45±31.11	59.06±20.53	38.88±18.05	<0.01[b]
sT	(pg/ml)	3.69±2.27	3.40±2.27	2.06±1.27	<0.05[b]
PRL	(ng/ml)	22.01±12.90	21.38±11.35	22.04±9.71	NS
F	(µg/dl)	22.44±7.67	21.21±6.87	15.68±5.05	<0.001[b]
ACTH	(pg/ml)	36.48±22.12	32.31±20.33	24.54±15.77	NS
DHEA-S	(µg/dl)	307.90±127.90	266.90±122.10	263.00±119.10	NS
17-OH P	(ng/ml)	2.44±2.37	1.77±1.09	1.48±1.42	NS
11-DOC	(ng/ml)	5.03±3.68	3.78±2.12	2.94±1.39	<0.01[d]

* One way ANOVA, NS: Not significant
a. Significant difference between PCOS and IH groups
b. PCOS and IH groups are significantly different than the controls
c. PCOS group is significantly different than IH and control groups
d. Significant difference between PCOS and control groups

subjects had significantly higher FSH levels when compared with PCOS and IH subjects ($p<0.05$ and $p<0.05$, respectively). Both tT and fT levels were found to be significantly lower in CS when compared with PCOS group and IH group (for both tT and fT, $p<0.01$ and $p<0.05$, respectively). PCOS group had higher levels of E_2 comparing with CS ($p<0.05$). Basal P, PRL, ACTH, DHEA-S and 17-OH P levels did not differ between groups, but patients with PCOS and IH had higher basal F levels than normal controls ($p<0.001$ and $p<0.001$, respectively). Basal 11-DOC levels were also found to be significantly higher in PCOS group than in CS ($p<0.01$), though no such significant difference between PCOS and IH groups or between IH and CS groups was found.

Basal A and DHT levels were measured only in patients with PCOS or IH and both of them were significantly higher in patients with PCOS than in patients with IH. The mean A levels were 5.61±0.47 ng/ml in PCOS and 4.35±0.34 ng/ml in IH subjects ($p<0.05$), while the mean DHT levels were 445.44±37.35 pg/ml in PCOS group and 349.99±26.85 pg/ml in IH group ($p<0.05$).

Table 2 shows the mean baseline and stimulated F, 17-OH P, 11-DOC and DHEA-S levels at 0, 6 and 8 hours after ACTH stimulation test in three groups. Peak levels and the percent increment in those parameters are also avaliable at Table 2.

The mean baseline and stimulated 17-OH P, 11-DOC, and DHEA-S levels in women with PCOS or IH were slightly, but not significantly, higher than control subjects. Furthermore, the peak and the percentage increment in 17-OH P, 11-DOC, and DHEA-S values were found to be similar in all three groups. On the contrary,

Table 2: Comparison of the baseline, stimulated, and peak levels of cortisol, 17-hydroxyprogesterone, dehydroepiandrosterone sulfate and 11-desoxycortisol with percent incremental ratios following ACTH administration (mean±SD)

		PCOS	IH	CS	p*
F_0	(µg/dl)	22.75±5.79	22.04±6.34	15.70±6.36	<0.001[a]
$F_{6\ hour}$	(µg/dl)	63.49±16.39	57.72±15.52	45.14±21.04	<0.001[a]
$F_{8\ hour}$	(µg/dl)	62.68±17.52	58.50±15.66	49.04±21.62	<0.05[b]
F_{peak}	(µg/dl)	66.95±17.33	60.90±16.52	49.13±21.63	<0.01[b]
$F_{percent\ increment}$	(%)	209.16±100.80	105.65±103.62	215.89±100.80	NS
17-OH P_0	(ng/ml)	4.94±12.52	2.16±1.30	1.83±1.58	NS
17-OH $P_{6\ hour}$	(ng/ml)	6.84±11.16	6.39±5.45	5.89±2.81	NS
17-OH $P_{8\ hour}$	(ng/ml)	7.78±11.65	7.35±4.15	6.97±2.95	NS
17-OH P_{peak}	(ng/ml)	8.57±11.44	8.42±5.28	7.10±3.04	NS
17-OH $P_{percent\ increment}$	(%)	276.30±305.73	429.95±481.64	490.52±354.87	NS
11-DOC_0	(ng/ml)	4.27±5.77	2.78±1.58	3.17±2.24	NS
11-$DOC_{6\ hour}$	(ng/ml)	9.03±4.89	8.38±5.07	7.96±2.80	NS
11-$DOC_{8\ hour}$	(ng/ml)	9.04±5.32	10.55±5.80	9.72±4.00	NS
11-DOC_{peak}	(ng/ml)	11.29±4.88	11.16±5.90	10.09±4.05	NS
11-$DOC_{percent\ increment}$	(%)	285.39±253.03	427.44±429.33	266.70±141.26	NS
DHEA-S_0	(µg/dl)	307.72±128.20	270.24±131.66	259.29±127.74	NS
DHEA-$S_{6\ hour}$	(µg/dl)	432.03±172.82	370.50±140.03	362.57±148.12	NS
DHEA-$S_{8\ hour}$	(µg/dl)	476.41±223.06	393.65±135.78	383.56±155.31	NS
DHEA-S_{peak}	(µg/dl)	466.24±162.67	406.18±146.93	388.29±154.09	NS
DHEA-$S_{percent\ increment}$	(%)	64.54±55.71	51.39±24.23	101.15±270.05	NS

* One way ANOVA, NS: Not significant, PCOS: Polycystic ovary syndrome, IH: Idiopatic hirsutism, CS: Control subjects, F: Cortisol, 17 OH P: 17-hydroxyprogesterone, DHEA-S: dehydroepiandrosterone sulfate, 11-DOC: 11-desoxycortisol

a. PCOS and IH groups are significantly different than the CS group

b. Significant difference between PCOS and CS groups

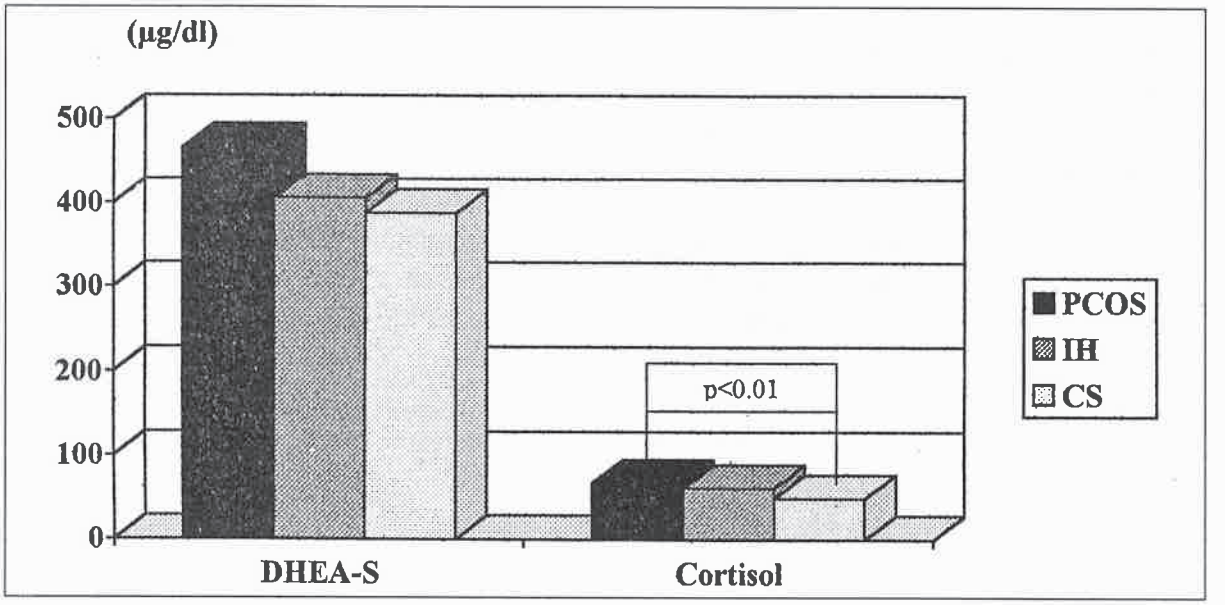
baseline and stimulated F levels, including peak values, were all found to be significantly higher in PCOS patients when compared with controls. However, no such difference was determined between PCOS and IH groups. Baseline and stimulated F levels at 6 hours after ACTH administration were also significantly higher in IH group when compared with CS, but stimulated F levels at 8 hours following ACTH stimulation and the peak F levels were not significantly different between IH and CS groups. Furthermore, percent increment in F levels after ACTH stimulation did not differ between groups, either. Figure 1 and 2 show the comparison of the ACTH stimulated peak levels of DHEA-S, F, 17-OH P and 11-DOC levels in three groups.

According to our criteria for LO CAH, two patients in PCOS group (6.45%) and four patients in IH group (12.50%) met the criteria for 21 OH deficiency. So among our 63 patients with hirsutism, the ratio of 21 OH deficiency was found to be 9.52%. No subject had ACTH stimulated 17-OH P level >13.4 ng/ml in CS group. Basal and ACTH stimulated 17-OH P levels in patients presumed to have 21 OH deficient LO CAH is seen at Table 3, with the comparison of the values of the other subjects without 21 OH deficiency among hirsute women

Table 3: Comparison of the basal and stimulated 17-hydroxyprogesterone levels in patients with 21 hydroxylase deficient late onset congenital adrenal hyperplasia and in hirsute patients without 21 hydroxylase deficiency, and in healthy control subjects.

		Subjects with 21 OH deficiency	Subjects without 21 OH deficiency	Healthy Controls	
		(n=6)	(n=58)	(n=28)	P*
17-OH P_0	(ng/ml)	16.96±26.05	2.06±1.49	1.83±1.58	<0.01
17-OH $P_{6\ hour}$	(ng/ml)	24.30±19.67	4.71±3.09	5.89±2.81	<0.001
17-OH $P_{8\ hour}$	(ng/ml)	21.38±22.54	6.08±3.47	6.97±2.95	<0.01
17-OH P_{peak}	(ng/ml)	26.18±19.96	6.60±3.29	7.10±3.04	<0.001
17-OH $P_{percent\ incement}$	(%)	341.06±256.67	357.16±425.05	490.52±354.87	NS

*One way ANOVA, NS: Not significant



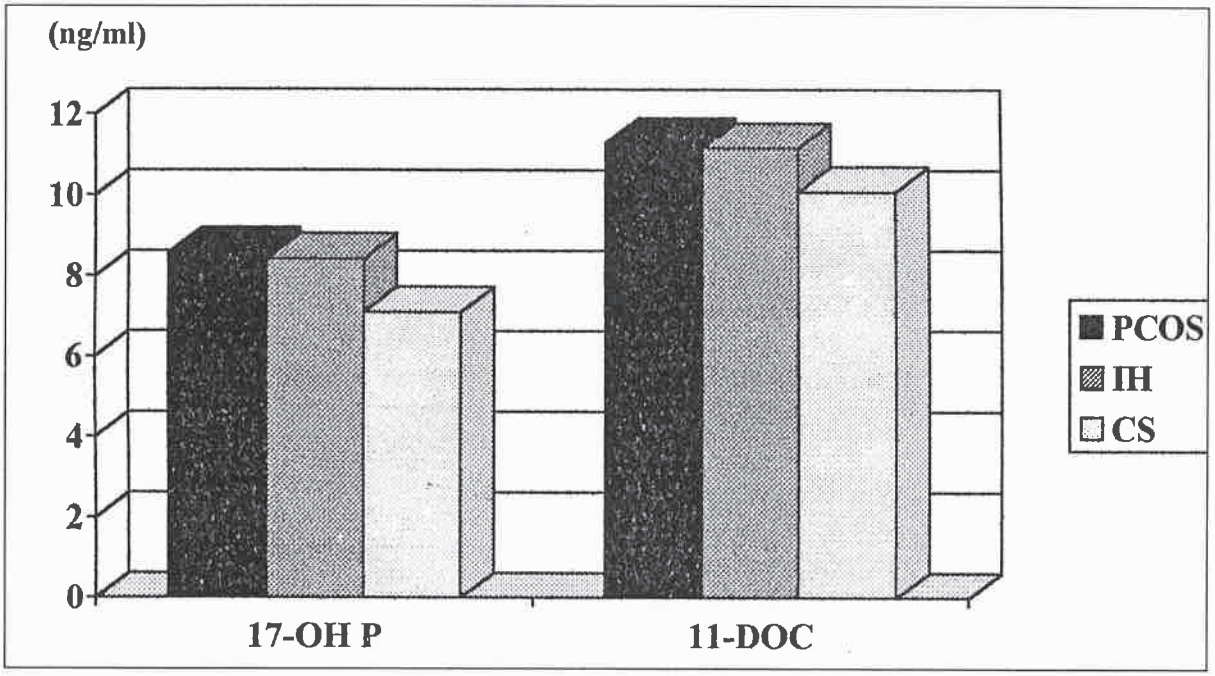
PCOS: Polycystic ovary syndrome, IH: Idiopatic hirsutism,
CS: Control subjects, DHEA-S: Dehydroepiandrosterone sulfate

Figure 1: Comparison of the ACTH stimulated peak dehydroepiandrosterone sulfate and cortisol levels in the groups

and normal controls.

Both basal and stimulated levels of 17-OH P were all found to be significantly higher in patients presumed to have 21 OH deficient LO CAH. In addition, peak 17-OH P levels were significantly higher in patients with 21 OH deficiency, as well. However, the percent incremental rate in 17-OH P did not differ between patients with 21 OH deficiency and hirsute patients without 21 OH deficiency or healthy controls.

Using a stringent diagnostic criterion for 11-β OH deficiency, we found no subject presumed to have 11-β OH deficiency in any of the groups. Surprisingly, one subject in CS group (3.57%) and two patients among PCOS subjects (6.45%) had



PCOS: Polycystic ovary syndrome, IH: Idiopatic hirsutism, CS: Control subjects

17-OH P: 17-hydroxyprogesterone, 11-DOC: 11-desoxycortisol

Figure 2: *Comparison of the ACTH stimulated peak 17-hydroxyprogesterone and 11-desoxycortisol levels in the groups*

DHEA-S response that exceeded the 2 SD of the mean of normal controls. So, it was not impossible to suggest that they had mild 3-β HSD deficiency. That one patient presumed to have 3-β HSD in CS group was evaluated individually and she had mild hirsutism with the hirsutism score of 6 though she had normal menstrual cycles.

Discussion

Abnormalities of adrenal function are common in women with hirsutism. Hyperandrogenic symptoms such as hirsutism, menstrual disorders and infertility are well known manifestations of CAH due to 21 OH deficiency, 11-β OH deficiency and 3-β HSD deficiency (23). Therefore, clinical presentation of LO CAH due to these enzyme deficiencies might be indistinguishable from the other clinical pictures of hyperandrogenemia, like PCOS and IH. In addition, sonographic abnormalities of the ovaries may be similar in women with PCOS and women with adrenal enzyme defects (24, 25). In many patients with PCOS, dexamethasone treatment can reverse symptoms of hyperandrogenism reflects that LO CAH and PCOS are overlapping. From a clinical point of view, these patients are not substantially different from the other hirsute women. So, women with PCOS or IH could be presumed to have adrenal enzyme deficiency.

Despite the necessity of molecular biology techniques for the exact diagnosis of adrenocortical enzyme deficiencies that causes CAH (16, 17, 26), ACTH stimulation test can provide useful information about adrenocortical abnormalities due to 21-OH, 11-β OH and somewhat 3-β HSD deficiencies. Recent studies have focused on the subject and ACTH stimulation test has become widely used to determine the prevalence of LO CAH in hirsute women. Unfortunately, there has been no certain criteria establishing the adrenocortical enzyme deficiencies yet. Moreover, the prevalence of LO

CAH largely depends on the ethnic composition of the studied population. These reasons can explain the different results in different studies. Speiser et al found the incidence of late onset 21-OH deficiency 3.7% in Ashkenazy Jews, 1.9% in Hispanics and almost zero in most Caucasian populations (27). Carmina et al found the prevalence of 21-OH deficient LO CAH 3.6% and 11-β OH deficient LO CAH 0.6% of 692 hirsute women in the Mediterranean population (28). Conflicting results for the prevalence of 3-β HSD deficient LO CAH in women with hirsutism are also present, as well (13-15).

In the current study, we tried to investigate the possible role of adrenal gland in PCOS and IH. Beside this, we measured ACTH stimulated 17-OH P, 11-DOC, and DHEA-S levels so as to find out the prevalence of 21 OH, 11-β OH and 3-β HSD deficiencies in our patients with clinically known PCOS or IH. Using a diagnostic criterion of 17-OH P>13.4 ng/ml following ACTH administration (which is over the 95th percentile of our controls), in our study, six out of 63 patients with hirsutism presented ACTH stimulated 17-OH P level over this value; this represents a 9.54% incidence of late onset 21 OH deficient CAH. Of these six patients, two of them were in PCOS group (with 6.45% incidence) and four of them were in IH group (with 12.5% incidence). In contrast with the previous studies held in the same geographic area, we found no case with 11-β OH deficiency. The prevalence of late onset 11-β OH deficiency was reported to be 6.5% among hirsute patients and 8.4% among patients with PCOS in Central Anatolia and in those studies no case presumed to have 21 OH deficiency was found (12, 29). Our results are just the opposite of the Kayseri group. They thought that the prevalence of LO CAH due to 11-β OH deficiency among Turkish women with PCOS and IH is relatively high, but it is hard to insist on that finding on the base of our results. It is already a well known matter that 21 OH deficiency is the most frequent form of all CAHs (27, 28, 30-33). In addition, Azziz et al reported that exaggerated 11-DOC response to adrenal stimulation (which is taken as diagnostic criteria for 11-β OH deficiency) are not always suggestive for the 11-β OH deficiency (11), because of a positive correlation between the basal and stimulated levels of F and 11-DOC. Other investigators also have observed an exaggerated F response to adrenal stimulation in hyperandrogenism, in combination with an exaggerated 17-OH P (34), 17-hydroxypregnenolone (35), and dehydroepiandrosterone response (36). So, hyperandrogenic patients with higher basal and poststimulation 11-DOC levels may also demonstrate higher basal and stimulated F levels. Similarly, in the study of the Kayseri group, the basal F level of the women with PCOS was found to be significantly higher than the control subjects, but they did not determine the stimulated F levels after ACTH administration (12, 29). We also demonstrated that basal and ACTH stimulated F levels were significantly higher in women with hirsutism when compared with normal controls. Although we have found no subject with exaggerated 11-DOC response, the only higher basal and stimulated F levels in our study groups may be the result of adrenal hyperactivity in these patients. On this occasion, we think, our results reflects the real prevalence of LO CAH in hirsute women in Central Anatolia. In our opinion, the real mechanism for hyperandrogenemia, at least in some of the hirsute women, depends on the adrenocortical hyperactivity. 21 OH deficient LO CAH may also be a reasonable factor in hirsutism. So, it is important to recognize 21 OH deficient LO CAH in women with PCOS because low dose steroid therapy may improve fertility, menstrual rhythm and hirsutism in those patients (19, 37).

In spite of the fact that, we could not monitorize our patients for 3-β HSD deficiency, exaggerated DHEA-S response (which exceeded 2 SD of the mean of the control subjects) with normal or minimally high 17-OH P rise after ACTH stimulation plus normal or high basal A levels and normal or low basal 11-DOC levels were taken in favour of possible mild 3-β HSD deficiency, in our study. In PCOS group, three patients showed exaggerated DHEA-S response

to ACTH stimulation but one of them showed exaggerated 17-OH P response as well, and she was accepted to have 21 OH deficiency. So two out of 31 patients (6.45%) with PCOS were thought to be presumed mild 3-β HSD deficiency. Interestingly,. one of our control subjects fullfilled the same criterion but it is questionable that she has 3-β HSD deficiency or not, because we did not measure the basal A levels of our controls. On the other hand, when we studied that patient individually, we realized that her hirsutism score was 6 and maybe she will be hirsute in a recent future.

In conclusion, the present study shows that LO CAH is not a rare disorder among hirsute women whether they have PCOS or IH. The most frequent form of LO CAH seems to be due to 21 OH deficiency in Central Anatolia. It must be taken into consideration since it is a well known CAH type in which steroid therapy is effective. Mild 3-β HSD deficiency may also be an underlying cause for hirsutism and it may be seen without any clinical presentation. According to our data, it is doubtless that adrenal hyperactivity is the main reason of hyperandregenemia in women with hirsutism. To learn the relationship between adrenocortical enzyme deficiencies and hyperandrogenemic states, molecular biology techniques and hormonal analysis must be used together and investigations on large women population with PCOS or IH are needed to establish the soun diagnostic criteria associated with hormonal determinations.

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VALUE OF PLASMA VISCOCITY AS AN ACUTE PHASE REACTANT IN PATIENTS WITH PNEUMONIA

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SUMMARY

Purpose: *Plasma viscosity is determined by various macromolecules, eg, fibrinogen, immunglobulins, and lipoproteins. Eritrocyte sedimentation rate (ESR) and fibrinogen levels are well known acute phase reactants. We aimed to evaluate the correlation between plasma viscosity and fibrinogen levels and ESR in patients with pneumonia.*

Methods: *Nineteen patients (7 women, 12 men , mean age=56±12 years) with noncomplicated pneumonia were included in the study. Plasma viscosity, serum fibrinogen levels and ESR were measured in all patients before and after the antibiotic treatment.*

Results: *All patients were succesfuly treated after antibiotic administration (10±4 days). There were significant decrease in fibrinogen levels, ESR and plasma viscosity after antibiotic treatment. There was a statistically significant correlation between the decrease of plasma viscosity and fibrinogen levels (r=0.79, p<0.001) after treatment. The decrease in ESR was not correlated with the decrease in plasma viscosity and fibrinogen levels .*

Conclusion: *We have shown that plasma viscosity significantly correlates with fibrinogen levels in patients with pneumoniae. Although ESR significantly decreased at the end of the antibiotic treatment, it was still above the normal range. Where as plasma viscosity showed a sharp decrease to normal range at the end of antibiotic treatment. This finding has suggested that plasma viscosity can be used an earlier marker of healing. With the support of further large clinical studies, plasma viscosity can be used as an acute phase reactant in patients with pneumonia and in other inflammatory disease*

Key Words: *Plasma Viscosity, Acute Phase Reactants, Pneumonia*

ÖZET

Pnömonili Hastalarda Akut Faz Reaktanı Olarak Plazma Viskozitesi

Amaç: *Plazma viskozitesini fibrinojen, immünglobulinler, lipoproteinler gibi makro moleküller belirler. Klasik olarak bilinen akut faz reaktanları eritrosit sedimantasyon hızı (ESR), CRP, fibrinojen, lökositozdur. Bu calışmanın amacı akut faz reaktanı olarak bilinen fibrinojen yerine plazma viskozitesinin kullanılabilirliğini araştırmak. Yapılan çalışmalarda fibrinojen yüksekliği ile kardiak mortalite arasında anlamlı ilişki saptanmış, yine bu çalışmalarda plazma viskozitesi ile fibrinojen seviyesi arasında korelasyon saptanmıştır. İnflamatuar hastalıklarda da plazma viskozitesinin arttığı bildirilmiş.*

Materyal-Metod: *Yaşları 29-84 arasında (ortalama:56) olan fizik muayene ,laboratuar ve radyolojik bulguları lober pnömoni ile uyumlu 7 si kadın 19 hasta kabul edildi. Tedavi öncesi ve sonrası hastaların fibrinojen, ESR, plazma viskoziteleri ölçüldü.*

Sonuçlar: *Tedavi öncesi ve sonrası plazma viskozitesi ve fibrinojen düzeyi arasında pozitif korelasyon bulundu. Fakat plazma viskozitesi ile ESR arasında ilişki saptanmadığı gibi, ESR ile fibrinojen arasında da korelasyon saptanmadı.*

Tartışma: *Pnömoni gibi akut enfeksiyonlarda ve inflamatuar hastalıklarda ESR yerine plazma viskozitesinin daha anlamlı olabileceği gözlendi. Tedavi ile plazma viskozitesindeki düşüşler ESR den daha önce ortaya cıktığı için erken dönemlerde enfeksiyonun tedaviye cevabını değerlendirmede kullanılabilir.Plazma viskozitesinin enfekiyon hastalıklarında ve diğer imflamatuar hastalıklarda akut faz reaktanı olarak kullanılabileceği düşünüldü.*

Anahtar Kelimeler: *Plazma Viskozitesi, Akut Faz Reaktanları, Pnömoni*

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Plasma viscosity is influenced by diseases with alterated plasma protein composition, determined by various macromolecules, eg, fibrinogen, immunglobulins, and lipoproteins An elevated viscosity also significantly increases the risk of inflamatory diseases. Since the physician can both decrease and increase plasma viscosity, it should be determined parallel to therapy. Accordingly, plasma viscosity is one of the most important rheological parameters(1). increased blood and plasma viscosity has been described in patients with coronary and peripheral arterial disease. The strong positive correlation between plasma viscosity and fibrinogen has been reported in several studies(1,2). Erythrocyte sedimentation rate (ESR) and fibrinogen levels are well known as acute phase reactants. It has been shown that the increase in the fibrinogen and globulin contribute significantly to the rise of the plasma viscosity. It has been reported that SLE patients with more severe disease have higher serum viscosity values, suggesting that serum viscosity values may provide an important marker for disease severity(3). We aimed to evaluate the correlation between plasma viscosity and fibrinogen levels and ESR in patients with pneumonia.

Methods

Nineteen patients (7 women, 12 men , mean age=56±12 years) with noncomplicated pneumonia were included in the study. Patients who had coronary artery disease, peripheral arterial disease, chronic obstructive lung disease, connective tissue disease were not included in the study (Table 1). All patients had fever, increased white blood cell count and pneumonic infiltration on chest x-ray. Plasma viscosity, serum fibrinogen levels and ESR were measured in all patients before and after the antibiotic treatment. Blood samples were drawn without stasis from the antecubital vein with a 21-gauge needle in a single attempt. EDTA-blood was centrifuged at 3000 g for 15 minutes. Plasma samples were stored –20°C untill measurement. Before measurement these were centrifuged at 3000 g for 15 minutes again. All viscosity were measured at 37 °C. Brookfield DW-II viscometer was used to measure plasma viscosity. Sputum investigation and blood samples have been taken for isolation of causative agent.

Results

Baseline characteristics of patients and causative agents are presented in table-I. There were significant decrease in fibrinogen levels (4.95±0.72 g/L vs 3.72±0.67 g/L p<0.001), ESR (71±19 mm/h vs 37±10 mm/h p<0.001) and plasma viscosity (1.43±0.12 mPa.s vs 1.29±0.10 mPa.s, p<0.001) after antibiotic treatment. Pure water viscosity was measured 0.78 mPa.s There was a statistically significant correlation between

Table-1: Baseline characteristics of patients with pneumonia

Male/Female	12/7
Age (years)	56±12
Addmittance fever (°C)	38.7±0.6
White blood cell count (/mm^3)	17240±1850
Causative agent	6(31%)
S. Pneumonlae	5(16%)
Gram(-) bacil	1(5%)
Undetermined	13(69%)

Table-2: Erythtocyte sedimentation rate, plasma fibrinogen levels, and plasma viscosity of the patients with pneumonia

Variables (Mean)	Before antibiotic treatment*	After antibiotic treatment*
Erythtocyte sedimentation rate (mm/h)	71±19	37±10
Fibrinogen levels (g/L)	4.95±0.72	3.72±0.67
Plasma viscosity (mPa.s)	1.43±0.12	1.29±0.10

* vs after antibiotic treatment p<0.001

the decrease of plasma viscosity and fibrinogen levels (r=0.79, p<0.001) after treatment (Table-2). The decrease in ESR was not correlated with the decrease in plasma viscosity (r=0.35 p= 0.14) and fibrinogen levels (r=0.21, p=.408). (Table-3)

Discussion

Viscosity is a way to describe how much resistance a fluid exhibits when an attempt is made to make it flow. High viscosity means the melt is thick and resistance to flow is high. Low viscosity means resistance to flow is less. Plasma viscosity, a major determinant of blood flow in the microcirculation.(4) C-reactive protein (CRP), serum amyloid A (SAA), fibrinogen, erythrocyte sedimentation rate (ESR), leukocyte count, have been associated with inflammatory and infectious diseases (5). Several studies have reported a strong association between various markers of the acute-phase response and death from cardiovascular diseases and all-cause mortality (6). Erythrocyte sedimentation rate, C-reactive protein and leukocyte count have been increasingly used as inflammatory indicators in assisting disease management (7). An other investigation reported that the changes in the three major blood proteins, namely fibrinogen, albumin and globulin, and their effect on plasma and serum viscosity in SLE patients during the course of treatment. The concentrations of fibrinogen and globulin were significantly increased, while albumin was decreased in the SLE patients as compared with the control group. This increase in the fibrinogen and globulin contributed significantly to the rise of both serum and plasma viscosity . SLE patients with more severe disease had higher serum viscosity values, suggesting that serum viscosity values may provide an important marker for disease severity (3). Plasma viscosity and fibrinogen were also associated with incident coronary heart disease and stroke in a study of older men and women(6). The strong positive correlation between plasma viscosity and fibrinogen found by other authors (8, 9)

In this study there was a statistically significant correlation between the decrease of plasma viscosity and fibrinogen levels after treatmentThe decrease in ESR was not correlated with the decrease in plasma viscosity and fibrinogen levels (Table-3). Although ESR significantly decreased at the end of the antibiotic treatment, it was still above the normal range. Whereas plasma viscosity showed a sharp decrease to normal range at the end of antibiotic treatment. This finding has suggested that plasma viscosity can be used an earlier marker of healing. We have shown that plasma viscosity significantly correlates with fibrinogen levels in patients with pneumoniae.

In conclusion plasma viscosity can be used as inflammatory indicators in assisting disease management. With the support of further large clinical studies, plasma viscosity can be used as a acute phase reactant in patients with pneumonia.

Table-3: *Relationship between plasma viscosity and fibrinogen levels, erythrocyte sedimentation rate*

	Fibrinogen	ESR	Plasma viscosity
Fibrinogen			
Pearson correlation	1,000	0,201	0,795 **
Sig.(2-tailed)		0,408	0,0001
ESR			
Pearson correlation	0,201	1,000	0,352
Sig.(2-tailed)	0,408		0,142
Plasma viscosity			
Pearson correlation	0,795 **	0,352	1,000
Sig.(2-tailed)	0,0001	0,140	

** P<0,01

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AGE-SPESIFIC SEROPREVALENCE AND ASSOCIATED RISK FACTORS FOR HEPATITIS A IN CHILDREN IN ANKARA, TURKEY

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SUMMARY

This study was performed for evaluation of age-spesific seroprevalence of hepatitis A virus (HAV) infection and associated risk factors among children in Ankara, Turkey.Five hundred forthyfour children (320 male, 224 female) with ages ranging from 7 to 192 months who came to hospital for the treatment of non-gastrointestinal diseases without chronic or urgent medical illnesses were included to the study. Subjects were separated into 4 age groups. Each group consisted 136 subjects. Serum anti-HAV IgG was tested by commercial ELISA kits. The overall seroprevalence of HAV in the study population was 41.2 %. The prevalence of hepatitis A increased with age from Group 2 to Group 4 (p<0.001), Group (1) 44%, Group (2) 38 %, Group (3) 59 %, Group (4) 87 %. Among the potential risk factors for transmission, significant differences were noted with respect to age of the subjects, school and institution for mentally retarded children attendance, maternal and paternal education levels, monthly household income, crowding, and sanitary facilities. Only crowding living conditions had a significant correlation with seroprevalence (r=0.517, p<0.001). Of the various potential risk factors examined, logistic regression analysis indicated that, only the age of the subject was independently associated with increased hepatitis A seropositivity.

Key Words: *Hepatitis A, Seroprevalence, Children, Risk Factors*

ÖZET

Hepatit A Enfeksiyonunun Yaşa-Özgü Seroprevalansı ve İlişkili Risk Faktörleri

Bu çalışma çocuklarda HAV infeksiyonunun yaş spesifik prevalansını ve ilişkili risk faktörlerini belirlemek amacıyla yapılmıştır. Yaşları 7-192 ay arasında değişen, hastaneye gastrointestinal sistem dışı hastalıkları nedeniyle başvuran, acil ve kronik hastalığı olmayan 544 çocuk (320 erkek, 224 kız) çalışmaya alınmıştır. Her grup 136 kişi olacak şekilde dört yaş grubu oluşturulmuştur. Serum HAV IgG testi ticari ELISA kitleri kullanılarak çalışılmıştır. Bu çalışma popülasyonunda HAV seroprevalansı % 41.2 bulunmuştur. Seroprevalans Grup 1' de (7-24 ay) % 44, Grup 2' de (25-72 ay) % 38, Grup 3' de (73-132 ay) % 59, Grup 4' de (≥ 133 ay) % 87 bulunmuş, seroprevalansın Grup 2 ile Grup 4 arasında arttığı saptanmıştır (p<0.001). Bulaşma için potansiyel risk faktörlerinden çocuk bakımevinde kalma, okula gitme, anne ve babanın eğitim düzeyinin düşüklüğü, evin aylık gelirinin düşüklüğü, kalabalık evde yaşama ve kanalizasyonlu tuvaletin olmaması ile HAV seropozitivitesi arasında istatistiki olarak anlamlı ilişki saptanmıştır. Seropozitivite ile belirgin korelasyon gösteren tek faktörün ise kalabalık yaşama koşulları olduğu belirlenmiştir (r = 0.517, p<0.001). Lojistik regresyon analizinde seroprevalansla ilişkili bağımsız tek faktörün yaş olduğu ortaya konmuştur.

Anahtar Kelimeler: *Hepatit A, Seroprevalans, Çocuklar, Risk Faktörleri*

Hepatitis A is caused by the hepatitis A virus and is transmitted predominantly through the faecal-oral route. Hepatitis A transmission is highly correlated with low socio-economic status and poor sanitary conditions. The mean age at which hepatitis A virus infection has been shown to differ in developing and developed countries, with infections occuring in younger age groups in

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developing countries. Because the disease is underreported and the infection often goes unnoticed, the epidemiology is best defined by measuring humoral antibodies. Anti-HAV IgG presence represents the cumulative rate of infection, both current and past (1, 2). The aim of this study is to determine the age-specific prevalence of hepatitis A virus and associated risk factors in children in Ankara, Turkey.

Material and Methods

Children aged between 7 months and 17 years without chronic or urgent medical illnesses who came to hospital for the treatment of non-gastrointestinal diseases were eligible for the study. Subjects were divided into 4 groups according to age. Group (1) consisted of patients between 7 and 24 months of age, Group (2) 25-72 months, Group (3) 73-132 months and Group (4) ≥ 133 months of age. Each group included 136 patients. A history of any serious and chronic medical illness was taken and a thorough physical examination was performed. After the informed consent was obtained, a questionnaire was completed by the child' s parent or guardian and blood was collected. Sera were separeted from a 3-5 ml venous blood sample from each subject and stored at - 20 C° until tested for IgG antibody to HAV. Information from questionnaire was included demographics, past history of icter, practice of cleaning, school or to any institution for mentally retarted children attendance, maternal and paternal education, monthly household income, crowding, household spaciousness, primary source of water, sanitation facilities. To decide to the practice of cleaning (dirty or clean) we examined the fingernails of the child. Maternal and paternal education levels were categorized as who did not complete primary school, completed primary school, completed secondary school or more. Total income of the household was expressed as a function of the Turkey regular minimum wage (<$ 100, ≥$ 100). Crowding was defined as the number of persons living the home and was categorized at two levels (≤ 4 or > 4 persons / home). The spaciousness of the home was calssified acoording to the number of the rooms (≤ 2, > 2). The source of water was classified as the utilization of the public system or bottled water or from a well. Sanitary facilities was classified as the presence of a flush toilet or pit toilet / outhouse.

Anti-HAV IgG was tested at Microbiology Laboratory of Sami Ulus Children' s Hospital by using EIA with ElAgen Anti-HAV kit-3rd generation (Biochem Immunosystem; Bologna-Italy).

Statistical Methods: Statistical analyses were performed using the computer package for Windows. Prevalence was assesed by the presence of anti-HAV antibody in the study group, and was stratified by age groups and explanatory variables. The associations between prevalence of anti-HAV antibody and age group and explanatory variables were evaluated by the Pearson χ^2. Statistical significance was defined as $p<0.05$. Sperman correlation test used to describe the significance of variables which found to be associated with HAV seroprevalence. A r value of 0.50-1 was considered significant. Logistical regression analysis was used to identify independent predictors of HAV infection.

Results

A total of 544 individuals- 320 males (58.8 %) and 224 females (41.2 %) included to the study. The mean age of children was 81.3 ± 56.7 months. Of the 544 children 228 (41.9 %) were seropositive for HAV-IgG. Seropositivity were 44, 38, 59 and 87 % in Groups 1, 2, 3 and 4 respectively. Anti-HAV seropositivity percentage between Grup2 and Group 4 increased significantly with age ($p<0.001$). Twenty-three (4.2 %) patients had a past history of icter. School attendance was associated with a higher seroprevalence. The rate of exposure to HAV was also significantly higher among children attending to an institution for mentally retarted children. The levels of mother's and father's education were also significantly associated with a lower seroprevalence ($p<0.05$ and $p<0.001$ respectively). Higher education levels of parents resulted with lower incidence of seropositivity among children. The seroprevalences among

those using pit toilets and those using flush toilets were significantly different being lower in the latter ($p<0.05$). Crowding had a significant association with seropositivity ($p<0.001$). Seropositivity percentage was significantly lower in small families with 4 and fewer members than in large families with more than 4 members. Of these various potential risk factors only crowding has a moderate correlation with seropositivity ($r=0.517$). The number of the rooms in the house was associated with the number of the persons in the house inversely ($r= - 0.54$). There wasn't any statistically significant difference in the seroprevalence of HAV antibodies between participants, according to the utilization type of water source. Furthermore, there was no significant association between seropositivity and the practice of cleaning of the child. The logistic regression identified the age of the participant as independent factor which significantly associated with HAV seropositivity. Seropositivity rates according to the demoghraphic and enviromental characteristics of the participants are shown in Table 1.

Discussion

The seroprevalence rates of hepatitis A in the children are lower in developed countries compared to our results (3-5). In developing countries, where sanitary and hygienic conditions are relatively poor, exposure to HAV infection is almost universal by early childhood. In contrast, in developed areas it is mainly an adult infection, and its spread is limited (1). Turkey is a developing country and previous serological reports from Turkey showed that majority of adults had HAV antibodies. The increasing anti-HAV IgG positivity with age can be related the enviromental factors (6). Our results showed that increased seroprevalence associated with age, with the exception of the 7-24 months age group had somewhat higher seropositivity than the 25-72 months age group. We believe that, it is due to maternal antibodies. A study that included 909 children in Istanbul in Turkey, indicated that anti-HAV IgG was increased with age. Anti-HAV IgG was demonstrated in 15.1, 26.7 and 49.6 % in children aged 6 months to 4.9 years, 5.0 to 9.9 years and 10.0 to 15.9 % years respectively (6). These seropositivity rates according to the age were low, compared to our results. This difference supports that, disease incidence varies geographically, with wide differences in prevalence from country to country, even within same country or city; the incidence may also vary with time (1). In developed countries increasing age was associated with increasing seroprevalence particularly among participants aged 30 years or more whereas in developing countries particularly among participants aged below 18 years reflecting the endemicity pattern. In a largest seroprevalence study that included 4462 subjects in 9 provinces representative of Turkey, Kanra et al. found recently anti-HAV seroprevalence was 70.2 % in children between 0-1 years, 42.7 % in those of 1-4 years, 57 % in those of 5-9 years, 70.6 % in those of 10-14 years, 82.5 % in those of 15-19 years, 90.9 % in those of 20-24 years and 91.1 % in the age group of 25-29 years. Authors concluded that hepatitis A is a moderately endemic in Turkey although seroprevalence differs from one region to another (7). In a serological study from England the overall seroprevalence was estimated to be 30.7 % and ranged from 9 % among those aged 1-9 to 11 % among those aged 10-19 before increasing to 17 % among those aged 20-29. After age 30 there was a sharper increase in seroprevalence with age to 73.5 % in those aged 60 and over (5). In a cross-sectional survey from Australia, approximately 50 % of patients were seropositive by the age of 40 years, while the rate in older people was 61 %. Seroprevalence dipped in the 10-14 years group, with a significant difference between this group and 15-19 years old, but not 5-9 years old (4). A population-based survey from the Netharlands, the seroprevalence increased from 2 to 3 % in the 1 to 9 years old to 86 % in the 75- to 79 years old (3). In contrast, the study from Palestine demonstrated that, by the age 6, 87.8 % of children had already acquired the infection. The prevalence increased gradually but linearly with age so that 97.5 of children were positive for anti-HAV by the age of 14 (8). It was reported from India, seropositivity increased with

Table 1: Seropositivity Rates According To The Demographic and Enviromental Characteristics of Participants

Characteristic	n	HAV seroprevalance (%)	P	r
Age (months)				
7-24	136	44		
25-72	136	38		
73-132	136	59	**< 0.001**	
≥ 133	136	87		
Past history of icter				
Yes	23	78.3		
No	521	40.3	**< 0.001**	
Practice of cleaning				
Clean	502	41.2		
Dirty	42	50	> 0.05	-0.092
School attendance				
Yes	233	53.6		
No	311	33.1	**< 0.001**	0.206
Institution for MR children attendance	6	83.3	**< 0.001**	
Maternal education			**< 0.05**	-0.204
Did not complete primary	104	59.6		
Completed primary	316	68		
Completed secondary or more	124	30.6		
Paternal education				
Did not complete primary	38	67.6		
Completed primary	293	47.4		
Completed secondary or more	213	30.9	**< 0.001**	-0.206
Monthly household income				
< $ 100	279	49.5		
≥ $ 100	265	34.2	**< 0.001**	-0.176
Crowding (persons/home)			**< 0.001**	**0.517**
≤ 4	237	33.3		
> 4	307	48.4		
Source of water			> 0.05	-0.035
Public system or bottled	515	42.2		
Well	29	38		
Sanitary facility				
Flush toilet	461	39.7		
Pit toilet/outhouse	83	54.2	**< 0.05**	0.11
Number of the rooms			> 0.05	
≤ 2		42.1		
> 2		41		

age from 52.2 % in the 1-5 year age group to 80.8 % in those aged 16 years or more (9). Another study from Saudi Arabia; hepatitis A seroprevalence showed 3 % in the < 6 years age group, 62 % in the 6-<8 years age group, 71 % in the 8-10 years age group, 83 % in the 10-12 years age group and 93 % in the 12-<18 years age group (10).

The low percent of the past history of icter indicated that the hepatitis A usually presents in an asymptomatic form in childhood.

The effect of the school attendance on increasing seroprevalence may be associated the increasing age and crowded conditions of the schools. Furthermore, transmission at day-care centers and schools manifests itself often in outbreaks (3). The prevalence of anti-HAV IgG antibodies was higher than the overall prevalence rate in the children who were resident of the institution for mentally retarded children. It had been reported that the instituonalized mentally retarded children were at increased risk of having hepatitis A infection compared to non-mentally retarded. It is also known that this high rate of infection is related to poor personal hygienc habits and the faecal-oral route of transmission (11, 12).

Mother' s education is also found to be significantly associated with a lower prevalence in the other epidemiological studies (13, 14). There are a number of ways in which maternal education contributes to the protection of children from infection. Low maternal education can play either a direct role (less educated women may have less knowledge of sanitary practices) or an indirect role (as a marker of overall low socio-economic status) (14). Our results also indicated that, higher monthly household income and father' s educational level reflecting the socioeconomic status, were lowering HAV seropositivity. In another studies, there were no significant association between HAV seroprevalence and monthly family income (9, 14).

Crowding living conditions in the home had been identified as a risk factor for hepatitis A. This could arise from socio-economic status, by greater possibility of contact, and the difficulty of maintaning hygiene in an overcrowded house. In a serological study, which investigated the epidemiology of hepatitis A, the risk of infection was greater among households with 2-3 members per room or more than 3 per room (14). In an another study, among children positive for HAV IgG, the average number of people in the house (5.5) and the average number of siblings (2.5) were significantly higher than in children who tested negative (15). We could not identified the number of members per room, but it was demonstrated that the number of the rooms in the house was associated the number of the persons in the house inversely. This finding supports the presence of the crowding living conditions and low socioeconomic status in our study group.

In our study , the type of water storage used in the household were not significantly associated with seropositivity. This finding suggests that contamination of water sources is not the main mechanism for hepatitis A transmission in the study population. There are studies that suggest a protective association between water supply and the seroprevalence of hepatitis A (7, 13). Household transmission of HAV occurs by faecal contamination of hands and fomites, and less commonly food and/or drinking water (14).

We could not demonstrated a significant association between practice of cleaning of the children and increased HAV seroprevalence. This finding does not support fecal-oral route of transmission. It likely associates the low number of subjects as evaluated dirty. Furthermore this variable may reflect only current cleaning condition.

It is possible that toilet facilities accounted for some cases of hepatitis A infection. A relationship was observed between the use of pit toilets or outdoors and infection with hepatitis A (1, 7). In contrast to our results, the study from Jamaika demonstrated that the type of toilet facility was not a good indicator for exposure to the virus (16).

In conclusion; the seroprevalence of HAV in

our study population from Ankara, Turkey is higher than in developed countries and similar to in developing countries. The age-spesific prevalence increased to 87 %, before the age of 17. Age and crowded living conditions were identified as the major risk factors for exposure to HAV. Residence in institution for mentally retarded children, school attendance, monthly household income and type of toilet were also associated to the higher seroprevalence. However practice of cleaning and source of water were not associated with exposure to HAV. Mother' s and father' s education levels were associated with lower seroprevalence Our findings are suggested that, prevalence of antibodies to HAV depends on the standarts of living conditions of the study population primarily. Seroprevalence could be declined among children with improvements in sanitation and socio-economic status in Ankara, Turkey.

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CARDIAC TROPONIN I IN ACUTE MYOCARDITIS TREATED WITH A 12-HOUR INFUSION OF HIGH DOSE INTRAVENOUS IMMUNOGLOBULIN

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SUMMARY

We report a successful outcome on an acute fulminant myocarditis treated with 12-hour high-dose (2 g/kg) intravenous immunoglobulin in a 9-month-old girl. We achieved rapid clinical and myocardial functional improvement in this patient. Cardiac Troponin I (cTnI) levels also rapidly declined to normal levels in response to intravenous immunoglobulin (IVIG) treatment. Cardiac Troponin I levels showed clear correlation with myocardial functional parameters during short-term follow-up of the patient. We conclude that high dose IVIG is very effective in acute fulminant myocarditis and cTnI is a useful marker to assess cardiac injury in these patients.

Key Words: *Myocarditis, Cardiac Troponin I, Immunoglobulin*

ÖZET

Akut Myokarditte Kardiak Troponin I

Biz 12-saatlik infüzyon şeklinde uygulanan yüksek doz (2 g/kg) intravenöz immünglobulin ile başarıyla tedavi edilen akut fulminant myokarditli 9 aylık bir kız hasta sunduk. Bu hastada klinik ve myokardial fonksiyonlar kısa sürede düzeldi. İntravenöz immünglobuline (IVIG) cevap olarak Kardiak Troponin I(cTnI) hızla normal düzeye döndü. Bu hastanın kısa süreli izleminde cTnI ile myokardial fonkisyon parametreleri arasında belirgin bir korelasyon vardı. Biz bu hastada akut fulminant myokarditte yüksek doz intravenöz immünglobulinin çok etkili olduğuna ve cTnI'nın kardiak hasarda kullanılabilecek bir belirteç olduğu sonucuna vardık.

Anahtar Kelimeler: *Myokardit, Kardiak Troponin I, İmmünglobulin.*

Acute myocarditis is an acute nonischemic inflammatory or immunologic response of the myocardium with various unknown causes. The course of acute myocarditis is very diverse, and it is sometimes difficult to make an early diagnosis and treatment. Therefore, acute cardiopulmonary collapse may develop soon after the diagnosis.(1)

There are few reports in paediatric literature regarding the troponins in detection of acute myocarditis. Cardiac isoforms of troponin-I (cTnI) are only expressed in cardiac muscle. Although the cTnI is a structural protein that is found in the striated muscle cell, bound the thin filament, a small percentage (3-4%) exists free in the cytoplasm. The increase in troponins (>0.5 ng/ml) were shown to be very sensitive (100%) in the myocardial infarction (AMI). However their specifity was lower (78%) compared to specifity MB fraction of total creatine phoshokinase (CPK-MB) (92%).(2,4) Cardiac isoforms of troponin-I also elevates in sepsis, septic shock, systemic inflammatory response syndrome (SIRS) and hypovolemic shock without coronary artery disease or myocarditis.(5)

The approach to treating acute myocarditis involves supportive measures for severe congestive heart failure, including inotropic support, preload and afterload reduction.(1,6) The role of corticosteroids for treatment of acute viral myocarditis is still controversial. In a small series of paediatric patients, treatment with prednisone (2 mg/kg daily) was effective in reducing myocardial inflammation and improving cardiac funtion(7,8). However, relapse

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may occur when immunosupression is discounted. Trials is currently under way evaluating the efficacy of intravenous gammaglobulin. We present a successful result on a myocarditis in a 9-month-old girl treated with 12-hour high-dose (2 g/kg) intravenous immunoglobulin.

Case Report

A 9-month-old girl who had been previously evaluated due to fever of unknown origin. Although extensive search was carried out no discernible aetiology has been found. She presented to our hospital with 2-days history of paleness, malaise, drowsiness, decreased oral intake and deterioration of general situation. She was admitted to paediatric intensive care unit (PICU) in shock. We couldn't take peripheric pulses and assess blood pressure. She was monitored, intubated and mechanically ventilated. We noticed the narrow QRS supraventricular tachycardia with a rate of 225 beats/min. Adenosine was given two times (100-200 µg/kg/dose). After the second dose ventricular fibrillation ensued. Electrical defibrillation was carried out four times then she returned with sinus rhythm. At the physical examination, after stabilisation, she appeared pale and had tachycardia with 3^{rd} heart sound. Her heart rate was 195 beats/min, blood pressure was 45/23 mmHg. The liver edge palpable 4 cm below the right costal margin. We administered dopamine, dobutamine and milrinone. After we began milrinone, patient's circulation was corrected and arrived normal urine output. Cardiomegaly and pulmonary venous congestion was demonstrated on chest X-Ray (cardiothoracic ratio [CTI] 0.58); (patient's CTI was 0.49 twenty days ago). An electrocardiogram (ECG) was performed which demonstrated sinus tachycardia (195 beats/min), globally low voltage and nonspecific ST-T wave changes. The echocardiogram showed normal anatomy without pericardial effusion but demonstrated enlarged left ventricle (LV) and left atrium, hypocontractility of LV with diminished EF (Ejection Fraction) 36%, increased left ventricle end-diastolic dimension (LVEDD) of 40 mm and moderate mitral valve insufficiency.

Complete blood count at admission revealed; Haemoglobin 8.4 g/dl, white blood cell count 14 300/mm^3, Platelets 438 000/mm^3. Biochemical analysis showed; blood urea level 74 mg/dl, creatinine 0.8 mg/dl, potassium 8.3 mmol/L. Her arterial blood gases were pH 6.94, pCO_2 32.7 mmHg, pO_2 43.7 mmHg, HCO_3 6.9 mmol/L. Peritoneal dialysis was started at third hour after admission to paediatric intensive care unit because of uncontrolled severe metabolic acidosis and hyperkalemia. Cardiac enzymes demonstrated an elevated creatine phosphokinase (CPK) at 2157 IU/L, CPK-MB 34 IU/L, LDH, SGOT, SGPT were also elevated. The cTnI, which was measured using an enzyme-linked immunoassay with specific monoclonal antibodies, was markedly elevated at 12 ng/ml (normal <0.2 ng/ml). Virus titer determination including cytomegalovirus, Epstein-Barr virus in the blood samples and enteroviruses in stool sample at all. Blood carnitine level and urine organic acids were normal. Although therapeutic measures including mechanical ventilation, peritoneal dialysis, inotropic support with dopamine, dobutamine and milrinone were done patient's clinical situation was not improved sufficiently. Tachycardia with 3^{rd} sound, hypotension, LV hypokinesis with low EF, were continued. CPK-MB and cTnI had also been raised. Due to insufficient response to the classic treatment measures a 12-HDIVIG (2 g/kg, infusion over 12 hours) was promptly administered in addition to inotropic agents at sixteenth hour from admission to our unit. The only adverse effect of 12-HDIVIG administration was fever (body temperature elevated to 39.5°C). Therapy was followed by serial cardiac and liver enzymes and echocardiographic measurements of left ventricular function (Table-1). The LVEF improved from 36% at baseline to 50% and the LVFS (Fractional Shortening) improved from 17% at baseline to 25% at 5 days after admission. Serial cTnI, CPK, CPK-MB, SGOT, SGPT analysis demonstrated a late increase with some persistence of the MB fraction. Cardiac Troponin I came back normal level at fifth day but CPK-MB

Table 1: *Cardiac enzymes and left ventricular function measurements before and after treatment with 12-HDIVIG.*

Measurement	Day of Treatment									
	-1	0	1	2	3	4	5	14	21	28
cTnI (ng/ml)										
(NR: <0.2)	10	12	7.5	3.2	0.8	0.6	0.3	0.0	0.0	0.0
CPK-MB (IU/L)										
(NR: 0-25)	34	215	186	190	164	95	67	56	21	15
CPK (IU/L)										
(NR: 0-170)	2157	5959	3250	1254	533	263	234	155	24	20
SGOT (IU/L)										
(NR: 10-49)	1475	2397	535	487	268	124	114	71	68	43
SGPT (IU/L)										
(NR: 10-37)	1016	1557	947	757	597	323	295	43	36	32
LVEF (%)	36	36	42	42	43	45	50	44	49	46.4
LVSF (%)	17	15	21	20	21	24	25	22	24.2	25.5
LVEDD (mm)	38.9	40.4	38.7	35.8	36.5	37.3	37.8	35.2	35.4	33.1
MVI	2^0	1^0	-	-	-	-	-	-	-	-

12-HDIVIG: 12-Hour High-Dose Intravenous Immunoglobulin, NR: Normal Range, CPK: Total Creatinine Phosphokinase, CPK-MB: MB Fraction of CPK, SGPT: Transaminase Serum Glutamic Oxalacetic, SGOT: Transaminase Serum Glutamic Pyruvic, LVEF: Left Ventricle Ejection Fraction, LVSF: Left Ventricule Shortening Fraction, LVEDD: Left Ventricle End-Diastolic Dimension, MVI: Mitral Valve Insufficiency.

returned normal ranges at about third week (Figure-1 and Table-1). In relation to the myocardial contractility, cTnI levels peaked first and declined first. Similarly, cTnI was better correlated with LVEF than the other cardiac injury markers.

She remained peritoneal dialysis only 16 hours, intubated for 4 days but when the patient was extubated, easily accomplished. The condition of the patient recovered rapidly after fourth day of beginning of 12-HDIVIG. Results of serum biochemical tests on day 21 of admission indicated normal cardiac enzymes. The patient's hospital course thereafter was unremarkable and she was discharged from the hospital by taking digoxin and captopril. The patient's follow-up chest x-ray, ECG and cTnI were normal. Follow-up echocardiogram demonstrated regression of LV dilatation and improvement of contractile function of LV (Table-1). The patient had resumed all of her normal daily activities.

Discussion

The troponin complex located on the thin filament of striated muscle and controls the interaction of thick and thin filaments in response to alterations in intracellular Ca^{2+} concentrations. It's composed of three protein components: Troponin I (TnI), which acts as an inhibitory subunit, troponin C (TnC); calcium binding subunit and troponin T (TnT), which is involved in the attachment of the complex to the thin filament.[3,9] Each of these subunits exists as a number of different isoforms that are associated

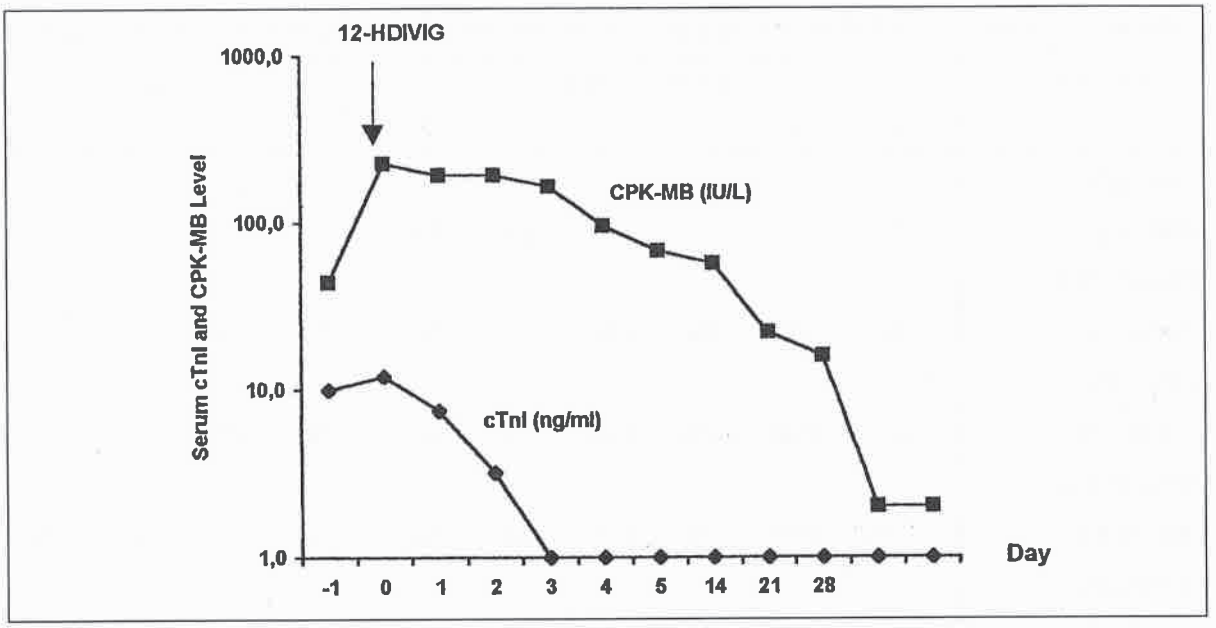

Figure-1: *Patient's serum levels of cardiac isoform of troponin-I (cTnI) and MB fraction of total creatine phoshokinase (CPK-MB) in response to the 12-hour high-dose intravenous immunoglobulin (12-HDIVIG) therapy in a child with myocarditis.*

with different muscle types (i.e., fast and slow skeletal muscle and cardiac muscle). Recently, several studies have raised an unexpectedly high percentage of elevated cTnI levels in ICU patients with (myocarditis, acute myocardial infarction) or without (sepsis, septic shock, systemic inflammatuary response syndrome, hypovolemic shock) heart disease (2,5,10). Furthermore, as a recent report suggests, a noninvasive test such as cTnI could potentially replace endomyocardial biopsy, the gold standard for the diagnosis of myocarditis. We measured cardiac troponin I (cTnI) isoform, CPK-MB in a patient to assess cardiac injury secondary to myocarditis and we specifically noticed the cTnI level increased and decreased to normal earlier than CPK-MB levels. We also showed that cTnI levels were fairly correlated with cardiac functions at echocardiography.

Results of controlled studies regarding the administration of high-dose IVIG for myocarditis complicating Kawasaki disease indicated that a single infusion of 2 g/kg during the first 10 days of illness was more effective than a regimen of 400 mg/kg for 5 days (2). The mechanism by which IVIG may improve myocardial dysfunction in myocarditis is unknown. IVIG could be effective by providing specific antibodies to viruses. An alternative mechanism of gamma-globulin's action may be modulation of the immune response, leading to decreased cardiac inflammation or to downregulation of proinflammatory cytokines that have direct negative inotropic effects.[7,9] Since myocardial damage in acute myocarditis is mediated in part by immunological mechanism, we also used a single 12-hour infusion of 2 g/kg IVIG to treat the myocarditis which had fulminant course shortly after sixteenth hours at admission of the patient. A study on 24-HDIVIG for treatment of acute myocarditis indicated that, compared with non-24-HDIVIG group, those treated with 24-HDIVIG had significantly smaller mean adjusted left ventricular end-diastolic dimension and higher fractional shortening in the period from 3 to 12 months (7).

Briassoulis G et al. reported a case with adenovirus myocarditis treated with high-dose

IVIG.[2] This patient's trend of ascending cTnI levels had reversed on commencing treatment. Likewise our patient's tendency of increasing cTnI levels was reversed first day of beginning of 12-HDIVIG treatment and at 5th day returned to normal range but downward course of CPK-MB begun on 3rd day of 12-HDIVIG treatment and CPK-MB returned to normal range just at 3rd week. Thus, our patient might have responded promptly to the HDIVIG; this is indicated by the consistent decline of the cTnI levels and improvement fractional shortenings attained within only a week period. In Kawasaki disease, the measurement of cTnI was shown to be useful serologic test for confirming the effectiveness of gammaglobulin therapy for the cure and prevention of cardiovascular abnormalities.[8]

In conclusion, the present case was shown the effectiveness of 12-HDIVIG in treatment of myocarditis, by demonstrated of decreasing cTnI levels in accordance with an improvement of cardiac functions. Therefore, the clinical relevance of cTnI has to be evaluated in further cases and studies.

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INTRAPLEURAL STREPTOKINASE IN THE MANAGEMENT OF PLEURAL EMPYEMA

Dalokay Kılıç* ✣ Murat Kara** ✣ Ulaş Kumbasar*** ✣ Şevket Kavukçu****

SUMMARY

Significant morbidity and mortality result from ineffective evacuation of pleural empyema. Standard treatment for pleural empyema includes; pleural drainage, and the use of antibiotics. This conventional treatment may not be effective for fibrin deposition and loculated empyema. Intrapleural streptokinase is an effective adjunct in the management of pleural emyema, and an alternative treatment of choice for surgery. In this article, we present two cases, which we performed intrapleural streptokinase with the diagnosis of multiloculated pleural empyema.

Key Words: *Intrapleural Streptokinase, Pleural Empyema*

ÖZET

Plevral Ampiyem Tedavisinde İntraplevral Streptokinaz Uygulaması

Plevral ampiyemin yetersiz tedavisi önemli bir morbidite ve mortalite nedenidir. Plevral enfeksiyonun standart tedavisi, plevral drenaj uygulanması ve antibiyotik kullanımıdır. Bu klasik tedavi şekli fibrin birikimi ve lokule plevral ampiyemde etkili olmayabilir. Standart tedavinin yetersiz olduğu durumlarda cerrahi olarak dekortikasyon uygulanmaktadır. İntraplevral streptokinaz tedavisi ise cerrahi tedaviye alternatif bir yaklaşımdır. Bu makalede multiloküle ampiyem tanısı alarak intraplevral streptokinaz uyguladığımız iki hasta sunulmuştur.

Anahtar Kelimeler: *İntraplevral Streptokinaz, Plevral Ampiyem*

Pleural empyema is an important entity in thoracic surgery with poor prognosis unless treated properly. It can cause sepsis and other complications which may increase morbidity and mortality. The treatment of choices in pleural empyema are thoracentesis, intercostal tube or pleural catheter drainage, video-assisted thoracic surgery (VATS) and open surgery (1, 2). Tube drainage often fails if the empyema is loculated with fibrinous adhesions, hence surgical treatment becomes necessary. Enzymatic debridement using intrapleural instillation of streptokinase is a minimally invasive option for loculated empyema and an alternative approach to surgery.

Herein we report two patients with multiloculated pleural empyema in which we performed intrapleural streptokinase with favourable outcome.

Case Reports

Case 1. 16 year-old boy who had undergone left posterolateral thoracotomy and lower lobectomy with the diagnosis of bronchiectasis four months previously. The patient was admitted to our clinic with cough and high fever

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complaints. On physical examination, no sounds were audible in the left lower zone of the thorax. Laboratory data revealed elevated levels of white blood cell count: 18.000/mL. A chest roentgenogram showed a blunt left sinus. Computed tomography of the chest showed multiloculated empyema pus in the left hemithorax. Thoracentesis confirmed the diagnosis of empyema and the culture was positive for Streptococcus pneumonia.

Case 2. 35 year-old man who had undergone left posterolateral thoracotomy and lower lobectomy with lingulary resection for bronchiectasis ten days previously. On physical examination, no sounds were audible in the left lower zone of the thorax. Laboratory data showed elevated levels of white blood cell count as 17.000 /mL. A chest roentgenogram showed a blunt left sinus (Fig. 1-a). Computed tomography scan of chest showed empyema pus in the left hemithorax (Fig. 1-b). Thoracentesis revealed a purulent pleural fluid, and the culture was positive for Staphylococcus aureus.

Both patients received systemic and specific antibiotic therapy during ten days (Case 1; Levofloxacin 1gr / day, Case 2; Teikoplanin 2 gr / day). An intercostal catheter (Pleurocan; Braun, Germany) was inserted into the pleural space in both patients. The catheters were flushed with saline solution (250 ml) in every 12 h. Streptokinase (Streptase; Farmatek, Istanbul, Turkey) 250.000 IU/ day in 50 ml saline solution were instilled into the pleural cavity, and the catheter was clamped for 4 hours. Both patients received this regimen for 2 days (Total dose 500.000 IU). Patients venous blood for prothorombin time (international normalized ration [INR], activated partial thoromboplastin time (aPTT), fibrinogen (FIB) were measured before and after streptokinase therapy. The results were within the normal limits in both patients. Catheters were removed when the drainage declined to below 50 ml daily, and the radiological re-expansion of the underlying lung was seen on follow-up chest X-rays (Fig. 2). The mean hospitalization duration of the patients was 2.5 days. The patients remain well mean 14 and

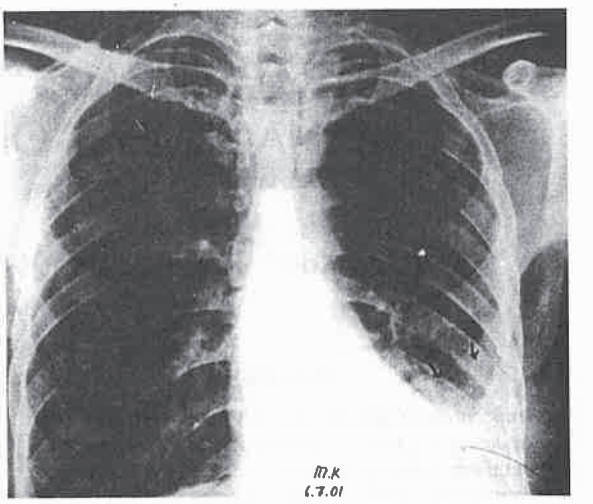

Figure1-a: *Chest roentgenogram showing pleural empyema*

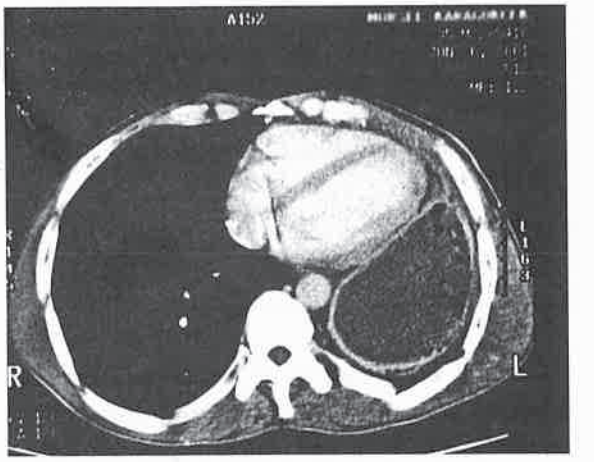

Figure1-b: *Computed tomographic scan of chest showing fluid collections of pleural empyema.*

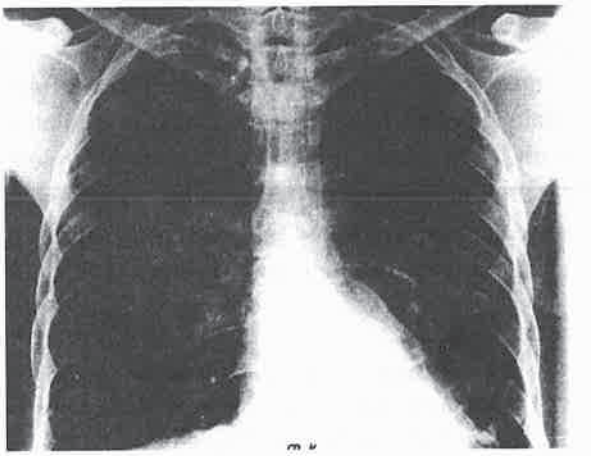

Figure 2: *Chest roentgenogram showing reexpansion of the underlying lung following intrapleural streptokinase therapy.*

11 months, respectively, following the intrapleural streptokinase therapy.

Discussion

Pleural empyema is an infection of the pleural space that can cause thoracic sepsis and other complications. It has been known since the times of Hippocrattes (3). Pleural empyema may develop in up to 44 % of patients with parapneumonia, and 10 % of patients in the postoperative period following pulmonary resection (1). Para pneumonic empyema can be caused by two mechanisms: obstruction of pulmonary lymphatics by inflammatory debris, which contaminates the pleural fluid by lymphatic transport of organisms from the focus of infection in the lungs, and direct extension of the pneumonic process into the pleural space. The second most common group are patients who have undergone operations on the lungs, mediastinum or esophagus.

The importance of adequate drainage of the pleural space was recognized in ancient times (3). The first line treatments of pleural empyema are adequate pleural drainage and systemic antibiotics. Empyema includes three phases, namely those are exudative, fibrinopurulent and chronic. Pleural drainage should be performed in the early phase because the development of pleural infection is a progressive process in which free-flowing exudative effusions can be transformed into a multiloculated empyema (4). Tube drainage inevitably fails if the fluid is loculated with fibrinous adhesions, thus a surgical intervention is needed. However, morbidity and mortality rates are greater in open surgical approaches (5, 6). Minimally invasive techniques such as VATS have been replaced with conventional surgical approaches recently (7). Despite the minimal invasiveness of VATS, it requires general anesthesia. However, the use of intrapleural streptokinase management can be established with local anesthesia. Thus, as being a less invasive procedure, the use of fibrinolytic agents such as streptokinase and urokinase may be the initial step and an alternative choice with minimal morbidity and mortality in the management of multiloculated empyema (8-10).

The recommended dose of streptokinase is 250.000-1.500.000 units in 100 ml of 0.9% saline; for urokinase the dose 100.000 units in 100 ml of 0.9% saline. We showed that a limited dose of 500.000 units of streptokinase daily is efficient in the management (11). Similarly, Davies et al. reported high success rate (85 %) with a limited dose of streptokinase in their series (10).

Streptokinase is administered with small-bore catheter and the patients can be mobile. This concern is presumably because of a theoretical risk of hemorrhage activated by local or systemic fibrinolysis. Intrapleural streptokinase has been shown not to activate systemic fibrinolysis in patients with empyema (1). Similarly, no differences in the laboratory tests were observed with respect to PT, aPTT, FIB between after and before intrapleural streptokinase therapy in our patients. Postinstillation fever, chest pain and specific IgG antistreptokinase antibodies occasionally may occur following streptokinase therapy (11). We did not experience any of the above complications in our cases. Likewise, Davies et al. and Taylor et al. reported no complications in their series (1, 9). Streptokinase was well tolerated in all patients as in the presented cases.

Intrapleural streptokinase therapy is an effective and safe adjunct in the management of complicated empyema and may reduce the need for surgery.

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USE OF BOVINE PERICARDIUM FOR CONGENITAL ABSENCE OF LEFT DIAPHRAGM

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SUMMARY

The bovine pericardium was successfully used for the repair of congenital absence of left diaphragm in a neonate.

In diaphragmatic agenesis (DA) there is a very large diaphragmatic defect requiring a prosthetic patch or muscle flap for closure, whereas in classical congenital diaphragmatic hernia (CDH), the defect is amenable to repair by direct primary suture. On the basis of different data, it is believed that DA is a subgroup of CDH and not a separate entity.

We present a case of the left sided agenesis of diaphragm in which bovine pericardium is used for repair who developed severe respiratory symptoms both in early and late postnatal period.

Key Words: *Diaphragmatic Agenesis, Bovine Pericardium*

ÖZET

Sığır Perikardı Uygulanan Doğumsal Sol Diyafrağma Agenezisi

Diyafrağma agenezisinde(DA) diyafragmanın tam yokluğu nedeniyle defektin protezle veya adele flepleri ile onarılması gerkmektedir. Halbuki klasik konjenital diyafragmatik hernilerde (KDH) diyafrağmatik kalıntıların primer olarak dikilmesi genellikle yeterlidir. Bazı verilere dayanarak DA'ler ayrı bir antite değil, KDH'lerin bir alt grubu olarak değerlendirilmektedir. Burada sol diyafrağma agenezisi olan ve bovin perikardı ile onarımı yapılan bir yeni doğanın erken ve geç dönemi tanımlandı.

Anahtar Kelimeler: *Doğumsal diyafrağma yokluğu ,sığır perikardiyumu*

Congenital diaphragmatic hernia (CDH) is associated with displacement of abdominal organs in to the thoracic cavity and the most serious form of these defects is the complete absence of hemidiaphragm.

Classification of CDH as diaphragmatic agenesis (DA) or classical CDH is based on findings at operation. With DA there is a very large diaphragmatic defect requiring a prosthetic patch or muscle flap for closure (1) . Owing a worse prognosis in diaphragmatic agenesis intensive preoperative preparation and postoperative ventilatory care are required when compared to classical CDH (1).

Case Report

A female full-term neonate weighing 3500 g was born by vaginal delivery to a 34 year old mother. Prenatally, ultrasound examinations failed to show any abnormalities. On delivery, she was intubated, ventilated, and an umblical catheter was placed. A chest x-ray showed a left–sided CDH. Pre-operative echocardiogram revealed persistence of left superior vena cava, which was the only associated cardiovascular abnormality. Radial artery blood gas analysis was made on admission and again when stabilized preoperatively. She underwent surgery within the first 12 hours of life. A laparotomy was performed

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revealing complete absence of the left diaphragm and all of the abdominal organs, with the exception of the kidneys, descending colon and rectum were in left thorax. Severe hypoplasia of the left lung was observed. The defect was repaired by suturing the bovine pericardium to the ribs with 000 polypropylen. Postoperative course was complicated by three weeks of ventilator therapy and persistence of oxygen need beyond neonatal period. Early in the post extubation period the infant was started on inhalation therapy comprised of salbutamol (0.15mg/kg qid) and budenosid (375 ucg bid). FiO_2 requirement of 0.3-0.4 in order to maintain SaO_2 of 95 % was persisted for 3 months. Contrast x-ray of the chest and the abdomen showed a repaired left sided DA with bovine pericardium at one year of age (Figure 1). Quantitative analysis of scintigraphic examination showed that 81% of the lung perfusion was provided by the right and 19% by the left lung (Figure 2). Though, the caloric and protein intake was provided by parenteral and enteral nutrition, growth of the infant was not optimal. The weight and height of the infant is currently was at the 3rd and 10th percentile

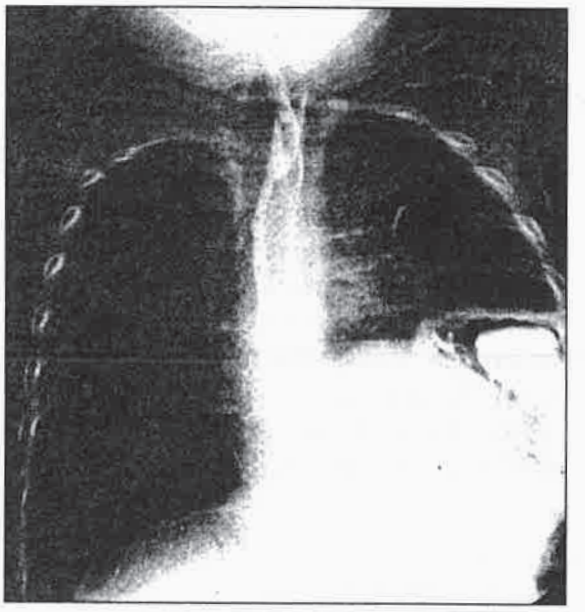

Figure 1: A chest and abominal x-ray with contrast material showed a repaired left –sided Diaphragmatic Agenesis with bovine pericardium at one year of age.

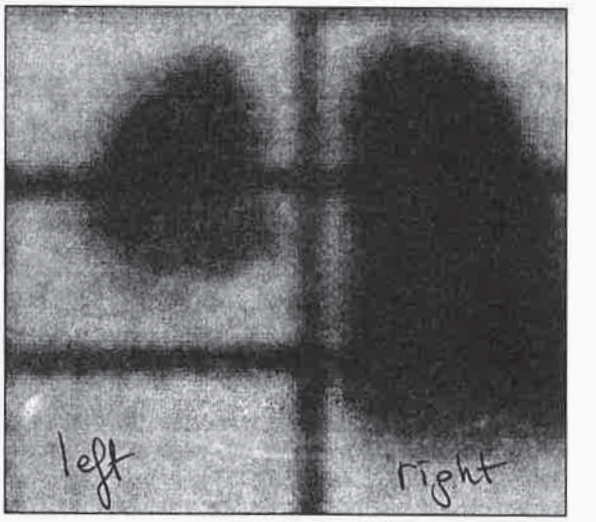

Figure 2: Quantitive analysis of lung perfusion scintigraphy showed 81% of lung perfusion provided by right and 19% by left lung.

respectively. She is now 12 months old, and free of supplemental oxygen therapy .

Discussion

Many operative techniques such as; suturing the liver(2), prerenal fascia(3), synthetic materials(4), and muscle flap from the anterior and lateral lower thoracic wall(5) have been proposed for the repair of this large defect of the diaphragm when the muscular remnants cannot be approximated. Organic materials have their disadvantage of technical availability, whereas synthetic materials have been suggested to demonstrate dehiscence(2-5). Despite these disadvantages, most of these materials especially synthetic ones were found to be acceptable. But the surgeons keep searching for a better prosthetic material. The bovine pericardium was used for the repair of congenital absence of left diaphragm in a newborn. Though this material have been used for hernia repair and as a bioprothesis for the closure of abdominal wall defects(6), present case is one of the first to report of its use in diaphragmatic hernia repair. It has been suggested that preserved bovine pericardium demonstrates similar charecteristics to dura; it was shown to be firmly incorporated

Table 1: Congenital Diaphragmatic Hernia-Diaphragmatic Agenesis

Reference	*Number of CDH* cases*	*Classical CDH*	*DA***	*Alive(number/%)*
1	23	15	8	4
6	37	27	10	4
10	38	36	2	2
8	108	92	16	3
11	109	101	8	
9	26	26		
	53	52	1	1
Total	394	303	44 (11)	13 (30)

*CDH: Congenital Diaphragmatic herniation

**DA: Diaphragmatic Agenesis

into the host tissue and maintains its strength over a prolonged period of time(6).

In the last 10 years period there is only a single case of DA among 53 CDH cases at our department. DA is relatively rare and posesses an unfavorable prognosis. The mean survival rate of 63 % indicates that despite decades of individual effort, the CDH problem is far from solved(7). Valantene and Brereton found in their review of 57 patients with CDH, 10 of whom had DA, that the degree of pulmonary hypoplasia rather than the size of the diaphragmatic defect was the main prognostic factor. They found little difference in the outcome of 10 infants with DA and 27 infants with CDH. However Tsang et al claimed that DA is associated with significantly higher morbidity and mortality when compared to classical postero-lateral defects of the diaphragm, and therefore should be recognized as seperate clinical entity. Baglaj et al.(8) reported that, of 108 babies with CDH, 16 (14.8%) were identified as having DA. Nine were subjected to operation and all required diaphragmatic replacement. Only 3 survived; thus, mortality in the DA group was 81.25 %, and among those who underwent surgery 66.6%.

Post operative course was complicated with three weeks of artificial ventilation and persistence of oxygen need beyond neonatal period in the present case. Fio_2 reqirement of 0.3-0.4 in order to maintain SaO_2 of 95 % was persisted for 3 months. From that period till 12 months, no further oxygen supplementation nor any medication for ventilatory support was needed.

On the basis of these data it is believed that DA is a subgroup of CDH and not a separate entity. Whether the large defect in the diaphragm is secondary to a greater volume of herniated contents or is the primary event leading to more herniation of contents is not known (1).Their observations support the hypothesis that DA occurs in the very early stages of embryonic life and may be attributed to developmental arrest of the septum transversum . Berman et al.(10) reported that, of 26 infants and children of CDH, 16 were misdiagnosed. Twenty-six patients were evaluated late presenting of CDH between 2 months and 12 years of age. It was collected that, of 394 CDH babies 44 were identified as having DA (Table1).

It is our impression that bovine pericardium is a good not even worse alternative to other prosthetic materials. More rapidly and firmly fixing to the chest wall, retaining its tensile strength for a long period of time, the formation of a cicatricial plate provided satisfactory stabilisation of the diaphram are the possible advantages of bovine pericardium in the repair of large defects of the diaphragm when the muscular remnants cannot be approximated.

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SYMPTOMATIC SACRAL TARLOV CYST: Case Report

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SUMMARY

Tarlov cysts are perineural cysts that usually arise in the extradural components of sacral or coccygeal nerve roots at the junction of the dorsal root ganglion. On rare occasions Tarlov cysts may be symptomatic. A case of symptomatic sacral Tarlov cyst is reported and appropriate patient selection for microsurgical treatment is discussed.

Key Words: *Microsurgical Treatment, Tarlov Cyst*

ÖZET

Semptomatik Tarlov Kisti: Olgu Sunumu

Tarlov kistleri, dorsal kök ganglionunun genellikle sacral veya koksigeal sinir köklerinin ekstradural komponetleriyle birleşme yerinde ortaya çıkan perinöral kistlerdir. Nadiren Tarlov kistleri semptomatik olurlar. Burada semptomatik bir sakral Tarlov kisti vakası sunulmuş ve mikrocerrahi tedavi için uygun hasta seçimi tartışılmıştır.

Anahtar Kelimeler: *Mikrocerrahi Tedavi, Tarlov Kisti*

Tarlov cysts are perineural cysts usually arising in the extradural components of sacral or coccygeal nerve roots at the junction of the dorsal root ganglion as described first by Tarlov in 1938. Sacral perineural cysts are usually found incidentally during imaging modalities or at autopsy (1). However, on rare occasions Tarlov cysts may be symptomatic and appropriate surgical treatment should be performed according to appropriate patient selection. The authors reported a case of symptomatic sacral perineural cyst diagnosed with magnetic resonance imaging (MRI) and microsurgical treatment performed by fenestration and imbrication of the cyst.

Case Report

A 20-year-old man presented with burning pain radiating from buttock to lateral thigh and left leg and bladder disfunction. The pain was worsening when standing upright or lying supine and was relieving at lying prone position. He has also experienced increased pain when valsalva maneuver performed. He did not complain weakness of his legs. The patient was significantly incapacitated, by these symptoms. Medical treatment by analgesic drugs were used before admission to our department but the patient has not revealed any pain relief.

The diagnosis of sacral perineural cysts were performed by computed tomography and MRI (Figure 1, 2). Preoperative urodynamic studies were performed and results were abnormal. According to the onset of bladder disfunction and exacerbation of radiculopathy with postural changes and valsalva maneuver we decided to perform surgery.

A sacral laminectomy was performed which revealed the cyst occupying the hollow of the sacrum. Microsurgical cyst fenestration and cyst imbrication was performed under operation microscope (Fig 3, 4). After surgery radicular pain and bladder control improved markedly. There

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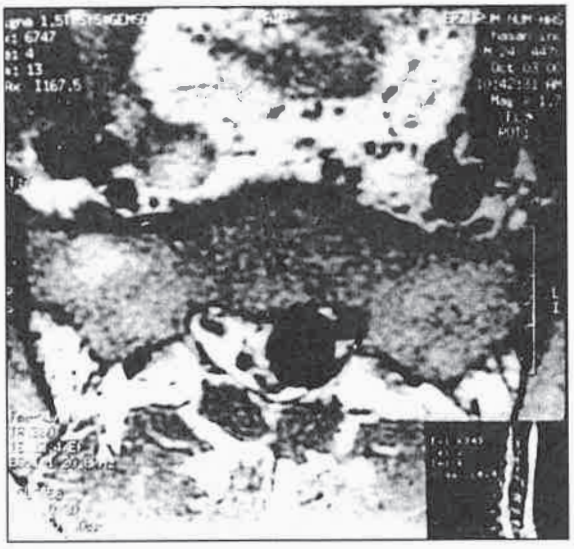

Figure 1: *T1-weighted axial image of sacral Tarlov cyst.*

Figure 2: T1-weighted sagittal image of sacral Tarlov cyst.

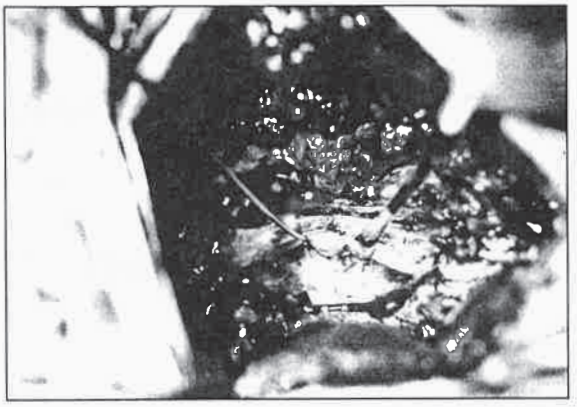

Figure 3: *Intraoperative photograph of Tarlov cyst before fenestration. Sacral nerve root is retracted. Arrowhead indicates the tarlov cyst.*

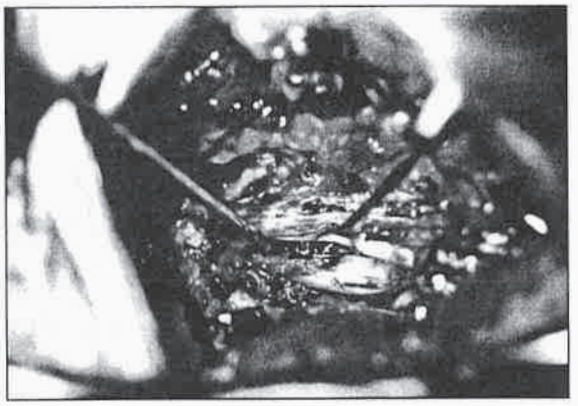

Figure 4: *Intraoperative photograph of Tarlov cyst after cyst fenestration and imbrication. Sacral nerve root is retracted and arrowhead indicates the imbricated Tarlov cyst.*

was no cerebrospinal fluid leaks and no new postoperative neurosurgical deficits. 3 months later the patient was complaining only local pain on his buttock.

Discussion

Sacral perineural cysts rarely become symptomatic. Tarlov described spinal perineural cysts while conducting an anatomic study for another purpose in 1938 (1). Since then less then symptomatic perineural cysts were found in 1% of incidentally discovered patients (2). The symptoms should be local or radicular pain, urinary incontinance, bladder disfunction, micturation disorders, cocygodynia, sensibility loss, dysesthesia or paresthesia or paresis according to the involved root (3).

Computed tomographic myelograms and MRI are useful for diagnosis (4,5). Tarlov cysts are best observed using T2-weighted MRI sequences. T1-weighted MRI sequences have also diagnostic value. The cysts are seen as fluid filled spaces in cerebrospinal fluid intensity at MRI sequences.

Treatment options of the Tarlov cysts are decompressive sacral laminectomy, cyst and nerve root resection, incision and drainage or the cyst with imbrication of the redundant nerve root sheath and lumbar cerebrospinal fluid drainage with lumboperitoneal shunting procedure, and cyst-subarachnoid shunt application (4,6-13). Appropriate patient selection is the key point of the surgical treatment. Medical treatment including analgesic and anti-inflammatory medication and physical therapy is the first step of all treatment. However, the onset of incontinence, bladder disfunction and the onset of impotence invites surgical intervention. Simple decompression has proven not to be successful. Cyst and nerve root resection often result in a neurological deficit (7). Praveen et al. observed that patients who experienced preoperative exacerbation of their radiculopathy with both postural changes and valsalva maneuvers were most likely to benefit from microsurgery (4). In our case according to bladder disfunction and radiculopathy with both postural changes and valsalva maneuvers we have chosen microsurgical treatment with cyst fenestration and imbrication. To prevent CSF lekage muscle grafts were placed epidurally over the fenestrated cyst. But we did not use any lumbar subaracnoid drain or perform lumbar puncture. However, if CSF leakage occurs lumbar subaracnoid drainage should be useful (4). The symptoms of the Tarlov cyst may arise from the compression of the involved root due to the intracystic hyperpressure. It has been hypothesized that the cyst neck serves as a valve and according to the systolic pulsation and patient's postural changes CSF enters the cyst but could not exit. When the cyst fills, the pain occurs; when the cyst deflates the pain reliefs (2, 14). So that the treatment modalities are based on this valve hypothesis. Incision and drainage of the cyst with imbrication of the redundant nerve reestablishes the cyst walls and the symptoms may resolve due to the disappearing of the intracystic hyperpressure. Lumbar cerebraspinal fluid drainage with lumboperitoneal shunting procedure and cyst subaracnoid shunt application are new treatment options. In multiple Tarlov cysts cases these treatment options should be useful.

In conclusion surgical treatment of the Tarlov cysts should be recommended to appropriately selected symptomatic cases.

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