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JOURNAL OF ANKARA MEDICAL SCHOOL Vol 20, No 2, 1998 61-64

A SIMULATION MODEL USING PATIENT DATABASE IN A PAEDIATRIC SURGICAL HOSPITAL UNIT

İsmail Haluk Gökçora* • Tolga Turna**

SUMMARY

A General Purpose Simulating System (GPSS) interface was used to simulate a hospital unit in terms of patient flow. The main purpose was to see, almost instantaneously, the long-term impact of decisions made on patient care. Another intention was to bring out a new and different point of view with regards to the existing hospital applications in Turkey. Patient wards(PW), surgical intensive care unit (SICU) and operating rooms (theatres) (OR) were only 16.94, 18.20, 6.65 per cent utilised respectively by sampling and computerised simulation. The results confirm the idle capacity of the unit.

Key Words: *Flow-chart, Hospital, Paediatric surgery, Simulation*

Although simulation models are common in the area of engineering sciences and that simulation in an hospital environemt is a rarity, the present attempt has been made to enable hospital managers to scrutinize and hopefully to find solutions for this research paper.

Existing governmental University Hospital management systems in Turkey lag far behind those private institutions who have fully recognised the importance of patient flow, the best use of time and beds with respect to the costs involved.

The General Purpose Simulating System (GPSS), a software available and applicable for simulating patient flow in a hospital environment, was hoped to establish a new view-point in analysing one of the existing University Hospital systems (1).

PATIENTS AND METHODS

Launched in 1984 and covering a period of twelve years to 1997, a joint venture was undertaken making use of GPSS, concerning the daily patient admissions, use of Patient Wards (PW), Surgical Intensive Care Unit (SICU) beds and Operating Room (theatre)(OR) time at the Paediatric Surgery unit, School of Medicine, University of Ankara and Faculty of Engineering, Middle East Technical University.

The daily admission rates of elective and non-elective patients were routinely stored in an electromagnetic media using an IBM PS/2 Model 8580-071 (Intel 80326) personal computer present at the hospital unit (courtesy of IBM Türk). The computer program thus used was dbase III+.

Though different surgical procedures require different time periods in the operating room and have a variability within themselves, depending on the individual case and the operating team involved, an approximate value was given for each specified class of operation (Tables 1,2).

The variability within operations was provided by sampling from the exponential distribution of the GPSS processor. The same sampling method was also used for the calculation of the post-operative hospital stay.

The existing beds at PW, SICU and allocated OR were accepted as valid and used throughout the model without any changes during the period of study not taking into consideration any political or environmental changes.

A six months' period was chosen at random by the GPSS processor in sampling the gross database used in this study.

Within the capabilities of the present software, every effort has been made to establish the model in such a way that it closely simulates the real system. Being a complex system however, "the patient flow system" required some simplifications (Figure 1).

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Table 1: GPSS distribution of paediatric surgical diseases archived for the randomly sampled six months and times assigned for preoperative, operative and recovery

(Diseases not encountered during the period sampled have not been included in this run.)

Disease entity	Frequency	Mean time in minutes Preoperative	Operative	Recovery
1. Oesophagial atresia	5	-	180	14400
2. Small bowel atresia	3	-	120	10080
3. Acute appendicitis	54	-	45	5760
4. Ileus	11	-	90	10080
5. Anal atresia	9	-	90	10080
6. Soft tissue abscess	3	-	30	5760
7. Diaphragmatic hernia	3	-	120	14400
8. Traumas	3	-	180	14400
9. Foreign bodies	6	-	75	4320
10. Torsion of testes	1	-	60	4320
11. Hepatosplenic disease	8	-	90	7200
12. Vascular disease	2	-	120	7200
13. Thoractomies	8	-	120	7200
14. Observation	10	-	-	5760
15. Necrotising enterocolitis	3	-	120	14400
16. Soft tissue biopsies	39	500000	30	360
17. Hydatid disease	2	4320	120	10080
18. Solid tissue biopsies	3	2880	60	2880
19. Thyroid disease	5	2880	90	5760
20. Lymphomas	6	2880	90	5760
21. Teratomas	2	5760	120	10080
22. Urinary disease	9	5760	120	7200
23. Hirschsprung's disease	6	14400	180	14400
24. Colonic polyps	21	4320	75	7200
25. Biliary atresia	-	10080	180	20160
26. Solid organ mass	7	5760	120	10080
27. Open vaginal processus	114	240	38	240
28. Genital disorders	11	14400	120	14400
29. Hygromas	1	2880	120	10080
30. Haemangiomas	-	5760	120	14400
31. GIS duplications	-	5760	180	14400
32. Extremity malformations	3	2880	90	14400
33. Sternocleidomastoid mass	6	2880	30	2880
34. Midline misclosures	8	1440	30	20160
35. Hypertrophic pyloric stenosis	5	1440	45	4320
36. GIS ostomies	10	1440	90	10080
37. Splenectomies	8	4320	90	7200
38. Vascular fistulas	2	4320	120	7200
39. GIS anomalies	2	10080	120	10080
40. Endoscopies	15	2880	60	2880
41. Dilatations	6	2880	30	2880
42. Sinuses and pits	1	2880	30	2880
43. Vaginal procedures	3	5760	30	5760
44. Gastro-oesophagial reflux	2	5760	120	14400
45. Circumcisions	52	240	20	240

Ten trial runs were made in order to draw meaningful results, using different random number seeds. These results were further statistically analysed to ascertain problem areas. Every simulation run was started with empty system conditions.

The model recorded patients who entered OR later than their allowable pre-operative time. The purpose of this was to estimate the operational system load and the effectiveness with which the existing system sources can meet demand.

The model was arranged in such a way that, it would simulate a year in a single run. Hospital stays more than three months were ignored, since they were rather rare.

The simulation assured the calculation and output of the following data:

1. Estimation related with the distribution of the daily patient admission. This was calculated by establishing distributions as sets of cumulative percentage functions called empirical distributions. The model calculated "the number of new patients admitted" for each simulated new day. The processor samples a value from a uniform distribution (explicitly defined in the program) each time a patient entered the SICU.

2. Database revealing the diagnosis of the admitted patients have also enabled the number of emergency cases. Each patient samples a different illness from its associated cumulative distribution function, mentioned in the prior item. The model then gave emergency patients a higher priority in admissions and operations. The logic of the model is shown in Figure 1.

Table 2: Distributions of paediatric surgery opertive times for a typical GPSS run.

Table From	Mean 59.11	STD.DEV 78.84	Retry 0	Range Minutes	Frequency
				0-15	210
				15-30	169
				30-45	78
				45-60	52
				60-75	25
				75-90	21
				90-105	33
				120-135	8
				135-150	14
				150-165	14
				165-180	10
				180-195	5
				195-210	8
				210-225	6
				225-240	4
				240-255	4
				255-270	2
				270-285	5
				285-300	3
				300-315	2
				315-330	2
				330-345	1
				345-360	9
				360+	8

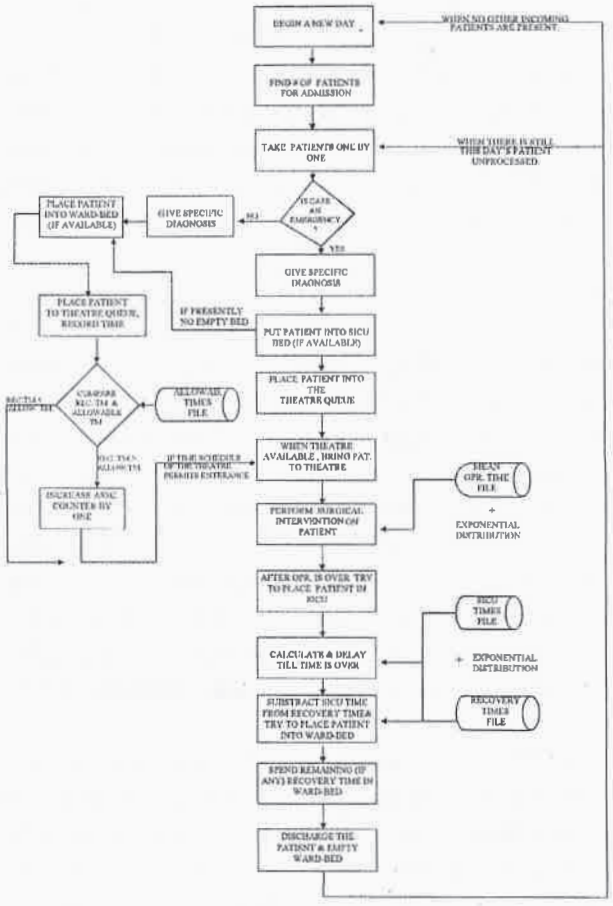

Fig. 1: The Patient Flow System.

Table 3: Distribution of paediatric surgery recovery times spent at patient ward in a typical GPSS run.

Table	Mean	STD.DEV	Retry	Range	Frequency
	5826.64	9802.58	-	0 minutes	3
			0 -	1440	188
			1440-	2880	46
			2880-	4320	48
			4320-	5760	33
			5760-	7200	29
			7200-	8640	18
			8640-	10090	12
			10090-	11520	10
			11520-	12960	11
			12960-	14400	10
			14400-	15840	4
			15840-	17280	6
			17280-	18720	8
			18720-	20160	5
			20160-	21600	2
			21600-	23040	1
			23040-	24480	5
			24480-	25920	6
			25920-	27360	1
			27360-	28800	1
			30240-	31680	3
			33120-	34560	2
			34560-	36000	2
			38880-	40320	1
			44640-	46080	2
			48960-	50400	1
			51840-	53280	1
			54720-	56160	1
			56160	57600	1

3. The simulation of the pre-operative preparation times was initiated as soon as the patient was admitted and put on the waiting list for surgical intervention.

RESULTS

The number of patients admitted to the unit in one simulated 12 months ranged from 574 to 655. The minimal and maximal for elective/non-elective patients were 439 and 512, 130 and 157 respectively. The number of days on which there were no "new patient admissions" in the unit ranged from 78 to 98. The probability of a case being an emergency was calculated as 26.5 per cent. At the end of each run the empty-beds ranged from 28 to 38.

The GPSS processor produced the mean and the standard deviation (SD) of all the patients admitted to the unit in each run and in all the runs the means were about one hour. The mean times produced by the runs were about 1100 to 3000 hours, with a SD ranging from 2000 to 3000 hours. The confidence interval constructed for the annual mortalities were 11.52, 16.08 with a 5% significance level (Table 3).

The recovery period spent by the patients in a ward-bed ranged from about 5000 to 6000 hours. These ranges were about 8000 to 8500 hours for SD. The discharge rate was 562 hours minimally and 633 hours maximally. Typical simulation model runs, which cover more than eight pages, produced by GPSS Report Generator has not been included in this manuscript to concur with the rules and regulations of the present journal.

Table 1., Table 2. and Table 3.

DISCUSSION

The runs have shown that a particular emphasis should be given to the OR. The administration can therefore see the impacts of different situations on the system by changing one or more of the parameters considered. For instance, by increasing the number of OR or PW, within a certain limit, the user can appreciate the general system performance by examining

the simulation output and can gain a clear idea of the system in its new condition. The quickest and most practical way to answer such "What-if.. ?" questions is by the careful and effective usage of this so-called simulation model. It is necessary to emphasise however, that it is most important to build and use the model in a very cautious manner. The keystone to the model lies within the parameters used and the management of the statistical nature of the data, which can exibit random results (2,3).

The ten analyses have shown the present capacity of the unit is well above actual incoming patient rate. In the current situation, the usage rate of the OR is also 10% below the available OR time, which further implies that, when all the patients are considered, the present capacity of the OR doesn't need any expansion or improvement. When the patient and surgical intervention queues are taken in to consideration, they likewise suggest no immediate problem. This is due to the fact that average patient queue numbers are well below the acceptable limits and the OR queue size is moderate (at any simulation run, no queue longer than 14 patients was observed). However, the number waiting for the OR was still considered high and it was decided to make a further concentration of effort on that particular sub-system.

Although the parameters used in this study are specific to the unit analysed, they can easily be modified or a new set of parameters just as easily defined to fit the simulation model of any other medical unit. The distributions used in the model were determined empirically and not theoretically. At first, this can be seen as a short-coming. As the main purpose of the model is the simulation of the surgical unit, the exclusion of such patients as ones from other medical units do not create a serious error. While, in real life systems, the patients may be accommodated in a different unit within the hospital, the present simulation model has however assumed the notion that the patient will have to wait for an empty bed at the surgical unit for his/her admission. Yet again, in the actual life system some patients may undergo further operations after their first. The present simulation model, has excluded this possibility for simplification intentions. In reality some patients may even undergo an operation and use the SICU bed even though hospital archives show the patient to be based at a different medical unit. Again these parameters haven't been considered in our model (4,5)

Further GPSS should be performed concentrating on the number and the time available for the activities performed by the staff, for the activities in the outpatients department utilisation, night duties and educational programs concerning both the doctors and nurses.

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THE COURSE OF THE ILIOHYPOGASTRIC AND ILIOINGUINAL NERVES IN THE ANTERIOR ABDOMINAL WALL AND THEIR RELATIONSHIP TO THE APPENDECTOMY INCISIONS*

İbrahim Tekdemir** • Mehmet Ersoy*** • Enis Cezayirli** • Alaittin Elhan**
Arzu Akan****• Ömer Fazıl Bilgin**** • Ahmet Gökhan Türkçapar****

SUMMARY

Incisions for appendectomy and other abdominal operations can cause injuries to the iliohypogastric and ilioinguinal nerves and inactivation of the shutter mechanism so that, these surgical procedures may be an etiologic factor in the developement of inguinal hernia. In this study, we aimed to research the effect of appendectomy incisions on the development of inguinal hernias by performing ilioinguinal and iliohypogastric nerves dissections. We studied the course of the iliohypogastric and ilioinguinal nerves in a total 12 formalin fixed cadavers (11 male, 1 female). In addition we reviewed 242 patients who were operated on for inguinal hernia between 1993- 1996 in Ankara University Faculty of Medicine Department of General Surgery. 21 of these previously underwent appendectomy. We concluded that iliohypogastric nerve might be dissected during Mc Burney or Elliot insicions in 17.3 % of these cases, but the ilioinguinal nerve was not dissected. However, iliohypogastric and ilioinguinal nerve were dissected in all cases with paramedian incisions. We supported these results by the cadaver findings anatomically and concluded that the type of insicion for appendectomy is closely related to the developement of inguinal hernias. We did not find any other study which the results were supported by demonstrating in cadavers dissections in the literature.

Key Words: *Appendectomy, Iliohypogastric nerve, Ilioinguinal nerve, Inguinal hernia*

Hernia, one of the most common disorders in man is afflicted, is known by for so many years. The first written source about hernias dating as early as 1550 B.C., is the Papyrus of Ebers of the ancient Egyptians (1). Incidence rates of primary hernias range between 0.6- 30 % in different series while that of recurrent hernias range between 1- 33.1 % (2).

Dissection of iliohypogastric nerve and ilioinguinal nerve leads to a defect in the closure mechanism and thus to hernia, suggesting a causal relationship between appendectomy insicions and hernia. This is shown with electromyographic studies on right side after appendectomy (3). Although electromyographic studies were performed upon 25 patients and did not correlate with prior appendectomy (4).

Briefly, inguinal hernias raise health care expenditures, cause loss of manpower and unnecessary occupation of hospital beds. In this study, we aim to show the courses of iliohypogastric and ilioinguinal nerves in the inguinal region and its anatomical relationship, if any, with the type of insicions used in appendectomy operations and with the development of inguinal hernia following these operations.

The inguinal canal is a musculoaponeurotic oblique tunnel through the anterior abdominal wall which transmits the spermatic cord in the male and the round ligament of the uterus in the female. In addition, ilioinguinal nerve passes through it in both sexes.

We think that the inguinal canal is like a rectangle prism which has four walls. The anterior wall of the canal is formed by the aponeurosis of the external oblique muscle. The superficial inguinal ring is situated in this wall. The posterior wall of the canal is formed by transversalis fascia. At the same time, it is reinforced by conjoint tendon medially. The inferior wall of the canal is formed the inguinal ligament which is formed by thicked and folded inferior edge of the aponeurosis of by the external oblique muscle. The superior

* This study was presented as a poster in the 4 th Clinical Anatomy Congress in France, September 3-5, 1997

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wall is formed by the arch that is formed by the inferior fibers of the internal oblique and transversus abdominis muscles. At the same time it is called conjoint tendon (5,6).

The inguinal canal in the lower part of the anterior abdominal wall constitutes potential weakness so that inguinal and femoral hernies may occur.

One of the protecting mechanisms of the inguinal canal is the shutter mechanism involving closure of the internal oblique and transversus abdominis muscles. During the increase of the intraabdominal pressure, this mechanism has a protective influence against developement of the inguinal hernia.

MATERIAL AND METHOD

In this study, we used 12 cadavers (11 male and 1 female) present in the Department of Anatomy, Faculty of Medicine, University of Ankara. 24 inguinal regions in 12 cadavers were studied. In order to make standard evaluation, the anterior superior iliac spine and pubic tubercle were identified and marked. Two transverse and two vertical lines were drawn from these points to limit a defined area because the incisions of Mc Burney, Elliot and paramedian are in this area.

First of all, in order to show the courses of iliohypogastric and ilioinguinal nerves within the defined area, we made an incision parallel to the inguinal canal throughout the skin. Then the incision was carried through the subcutaneous tissue, abdominal wall muscles were dissected and the nerves were identified. After that, we studied the courses of these nerves and their relation to Mc Burney, Elliot and paramedian incisions used during appendectomy. We reviewed 242 patients who were operated on for inguinal hernia in Ankara University, Medical Faculty, Department of General Surgery between 1993-1996 years retrospectively. 34 of them were women and 208 were men. The ages of patients were between 22-76 years. It was known that these patients had appendectomy operation or not in the past.

RESULTS

In all of the cadavers, the ilioinguinal nerve is identified within the area in the inguinal region, that is defined by the two vertical and the two transverse lines passing through anterior superior iliac spine and pubic tubercle (Fig. 1). At dissection in 20 of the 24 inguinal regions (82.7 %) in which it could be observed, the iliohypogastric nerve was always found within the defined area limits (picture 1), but in 4 inguinal regions (2 right and 2 left) (17.3 %) the nerve was outside the limits (Fig. 2). According to the courses of the iliohypogastric and ilioinguinal nerves, there is no signi-

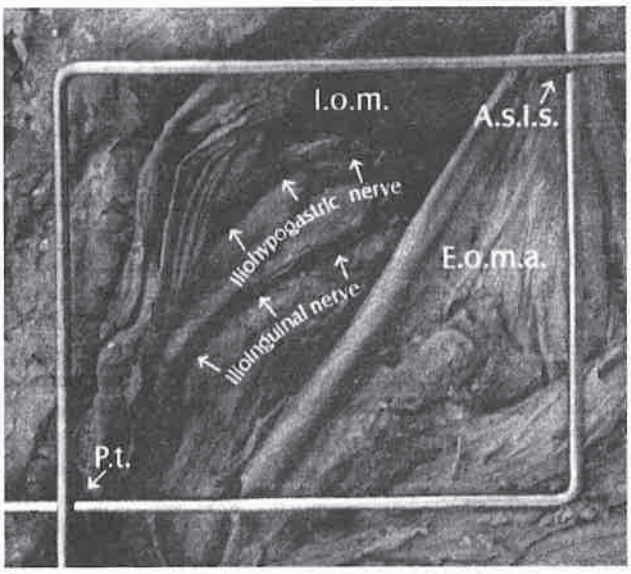

Fig. 1: The courses of the iliohypogastric and ilioinguinal nerves within the defined area on the left side.
I.o.m: Internal oblique muscle
E.o.m.a: The aponeurosis of the external oblique muscle.
A.s.i.s: Anterior superior iliac spine
P.t: Pubic tubercule

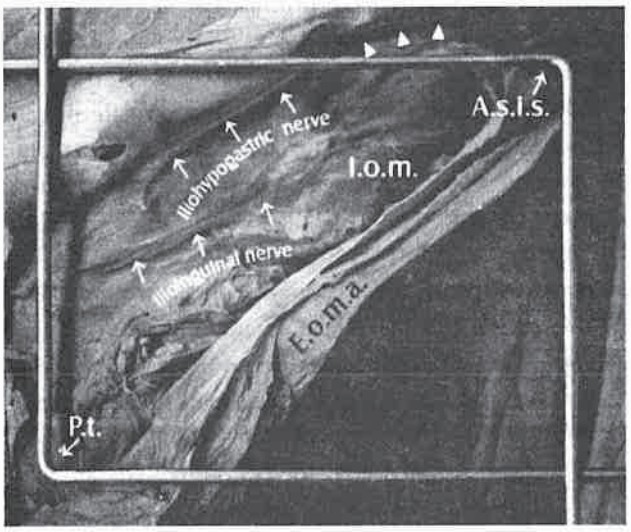

Fig. 2: The course of the iliohypogastric nerve out of the defined area on the left side.
I.o.m: Internal oblique muscle
E.o.m.a: The aponeurosis of the external oblique muscle.
A.s.i.s: Anterior superior iliac spine
P.t: Pubic tubercule
(The course of the iliohypogastric nerve out of the defined area is shown by three arrowheads)

Table 1: Association between appendectomy and subsequent development of an inguinal hernia that required repair

	Number of patients who had appendectomy (%) n=21	Number of patients who had not appendectomy (%) n=21	Total (%) n=242
Side			
Right	18 (85.7%)	148 (66.9%)	166 (68.6%)
Left	3 (14.3%)	73 (33.1%)	76 (31.4%)

ficant difference between the right and left sides on cadavers.

In the retrospective study, we observed that a total of 242 hernia were operated on University of Ankara, Department of General Surgery. 21 of these previously underwent appendectomy. Of these patients, 18 developed right inguinal hernia (85.7%), remaining 3 were left hernia (14.3%). 221 of them had not appendectomy. 148 of these patients had right hernias, 73 of them had left hernias (Table 1). We had no bilateral hernias in our series. Of the 18 patients with right inguinal hernia who previously underwent appendectomy, 9 (50 %)had Mc Burney, 1 (5.6 %) had Elliot and 8 (44.4%) had lower paramedian incision when we looked at operation scars. Of these all cases, 14 patients were indirect and 4 were direct hernia, on the right side. All of the hernias on the left side were indirect hernia.

DISCUSSION

Of the 21 patients who had appendectomies 18 (85.7%) developed right inguinal hernias compared with 148 (66.9%) of the 221 patients who had not. The right: left ratio was 6:1 in first group and 2:1 in the second group ($p<0.05$) (Table 1). Our figures are similar to that of Arnbjörnsson and Gue who found a threefold increase in the right:left ratio (7,8). The high rate of right inguinal hernia in their and our series would be explained by the fact that almost half of the appendectomies in their and our series had been through lower incisions. However, Leech et al., Malazgirt et al. and Scott at al. found no difference between the number of left and right sided hernias in patients who had appendectomies (9,10,11). Malazgirt, et al. found only one lower paramedian insicion of 42 patients (2.4 %) with right inguinal hernias who had had appendectomies previously, in their series, respectively (10).

One of the factors contributing to the development of inguinal hernias is the defect in the anatomy of the abdominal wall. Among these factors are insufficiency of the muscles in the inguinal region, abnormally wide deep inguinal ring, absence of conjoint tendon and defect in the shutter mechanism (12,13, 14).

During forced inspiration, to compensate the increase of intraabdominal pressure, the arcus formed by the free lower margins of internal oblique and transversus abdominis muscles closes upon the spermatic cord (or the round ligament in the female) like a shutter and prevents hernia formation (3,5,6).

Deficiency in the fiber of the internal oblique and the transversus abdominis muscles or denervation of these muscles produce deficiency in the closure mechanism. In an electromyographic study, it was proved that absence of contraction on the lower fibers of the transversus abdominis muscle in the inguinal region of the patients with inguinal hernia on one side. Same study was performed on the other side of the hernia and normal electromyographic activity was noted (3). The other electromyographic studies were performed upon 25 patients and abnormality signifying partial denervation was found in only three patients and did not correlate with prior appendectomy (4).

In recent researches, right inguinal hernia is found to be six times more common after appendectomies due to dissection of iliohypogastric nerve and ilioinguinal nerve (8). Hoquet found this ratio as 1/25 (15). The incidence of right inguinal hernia in patients who have undergone appendectomy is significantly greater than that in the general population. It is suggested that the most likely cause is injury to the segmental nerve supply to the inguinal musculature.

Mc Burney incision, that is used in appendectomy operations, passes through Mc Burney's point, which is located lateral one third of the distance from anteri-

or superior iliac spine to the umbilicus (16). In our study, in 17.3 % of cases iliohypogastric nerve is shown to be dissected during these commonly used incisions. Paramedian incisions, performed for perforated appendicitis, lies within the defined area. Thus, dissection of these nerves during paramedian incisions are more likely.

In conclusion, during Mc. Burney and Elliot incisions for the purpose of appendectomy, the possibility of injury to only iliohypogastric nerve is 17.3 % while it is almost 100 % in paramedian incisions. Thus, the type of incisions for appendectomy operations is closely related to the development of hernias and it is worth studying on.

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PROTECTIVE EFFECTS OF CATALASE PRETREATMENT ON LIPID PEROXIDATION INDUCED BY WHOLE-BODY GAMMA-IRRADIATION IN RATS*

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SUMMARY

In this study, we examined the protective effects of catalase pretreatment on irradiation-induced lipid peroxidation. Male albino rats were exposed to whole-body gamma-irradiation (total dose of 5Gy in one exposure which is toxic for rats). In the first experimental group, rats (n:12) were only exposed to radiation, in the second experimental group (n:12), catalase (150.000 IU/kg) was administered to rats before irradiation. The rats in the third experimental group (n:12) were pretreated with catalase before the sham-exposure. As control group, sham-irradiated rats (n:12) were used. The initial plasma malondialdehyde levels of irradiated, catalase pretreated plus irradiated, catalase pretreated plus sham-exposed groups did not significantly differ from that of sham-irradiated rats. On 10th day after the sham-exposure, sham-irradiated controls and catalase pretreated plus sham-exposed animals showed similar levels of this biochemical parameter. The latter plasma malondialdehyde level of sham-irradiated rats was 8.6 ± 1.8 nmol/ml and the latter value of irradiated animals was 30.9 ± 7.2 nmol/ml. These results showed that plasma malondialdehyde levels of irradiated rats were significantly higher than those of sham-irradiated controls ($p<0.05$). In catalase pretreated plus irradiated group, mean plasma malondialdehyde level was measured as 12.0 ± 4.1 nmol/ml. It was indicated that application of catalase before irradiation markedly reduced plasma malondialdehyde levels compared to irradiated rats ($p<0.05$). High doses of ionizing irradiation causes oxidative injury by producing free radicals. It was considered that lipid peroxidative effects of ionizing irradiation might be consist of general peroxidative changes in cellular membrane lipids of radiosensible tissues and in plasma lipoproteins. Catalase is an enzymatic component of antioxidant defense system and plays an important role in the prevention of biomolecules from oxidation by detoxification of H_2O_2. This study demonstrated that catalase pretreatment has a protective effect against lipid peroxidation induced by ionizing irradiation.

Key Words: *Radiation, Free radicals, Lipid peroxidation, Catalase, Antioxidants*

Oxidative stress has been defined as the inability of the cells to defend themselves against reactive oxygen species, resulting in oxidative injury (1-3). Several authors have reported that increased production of oxygen free radicals in tissues can result in oxidative damage of cells (1-9). In this mechanism, free radicals which are formed by oxygen, initiate peroxidation in biological membranes. The primary oxygen radicals are short-lived whereas the lipid peroxides are relatively stable (4,10-13). One of the best-characterized biological damage caused by free radicals is their ability to stimulate the chain reactions known as lipid peroxidation (3,4,8,10-14). When free radicals are generated excessively in organisms, their detoxification are insufficient and reactive oxygen species attacks to the fatty acid side-chains of the membrane phospholipids. Carbon-centered radicals formed by polyunsaturated fatty acid side-chains usually undergo molecular rearrangement to give conjugated diene structures. Following these reactions, lipid peroxidation products are generated. Since malondialdehyde (MDA) is one of the main products of lipid peroxidation, it is used frequently to evaluate the free radical induced oxidative damage (6).

* Some data in this study was presented at Proceedings of the XVI. International Congress of Clinical Chemistry, London, UK, p: 320, (8-12 July) 1996.

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Early studies suggested that ionizing irradiation caused tissue damage by a mechanism similar to that proposed for oxygen toxicity (13,15,16). Nowadays, it is well established that ionizing radiation is a potential source of free radical which not only react with DNA but also cell membrane components (12). Previous studies have shown that ionizing irradiation causes the increase in lipid peroxidation products in living organisms (12,13,17-19).

Knowledge of pathogenic mechanisms leading to ionizing irradiation-induced toxic effects could contribute to development of preventive treatments (12). Radioprotectants can not only be useful in protecting healthy tissues during human radiotherapy but can be beneficial to personnel engaged during peace time in "cleanup of radioactive accident area" and future spaceflights, as well (20). Some investigators reported that administration of antioxidants such as; superoxide dismutase and catalase intravenously had protective effects against free radical toxicity (2,5,7,9,15). Therefore, several authors suggested that radiation-induced oxidative damage may at least in part possibly be eliminated by antioxidants (1,11,12). The present study performed to examine possible protective effects of catalase pretreatment on lipid peroxidation induced by gamma-irradiation in plasma on rats.

MATERIAL AND METHODS

Animals: The experiments were performed using mature (10-12 week-old) male Albino rats (n:48). All rats were supplied with standard food and water ad libitum.

Experimental Design: The main aim of this experimental study was to evaluate the level of a lipid peroxidation product, MDA in plasma after whole-body gamma-irradiation of rats. We also would like to examine whether the pretreatment of catalase, a physiological free-radical scavenger enzyme, protects against irradiation-induced lipid peroxidation.

Experiments: Animals were randomly divided into four groups (number of animals given in parenthesis).

First experimental group was irradiated with single dose of 5Gy (n:12).

Second experimental group was pretreated with catalase before irradiation (n:12).

Third experimental group was pretreated with catalase before sham-exposure (n:12).

Control group was sham-exposed without irradiation (n:12).

Sham-exposed control rats and irradiated rats (1st group) were injected 1cc saline intraperitoneally. Rats in 2nd and 3rd groups were injected catalase (150.000 IU/kg) diluted with 1cc saline intraperitoneally 2 hours before the exposures.

Whole body irradiation and dosimetry: Food was removed from all animals 12 hours before irradiation. Fifteen minutes prior to irradiation, each rat was anesthetized with intraperitoneal injection of pentobarbital (30 mg/kg), resulting in a light anesthesia and relaxation. The animals were placed on their backs, aligning the vertebral column along the longitudinal line marked on the plastic plate. All legs and tail were firmly fixed by surgical tape. Then, animals of all experimental group were controlled radiographically for proper positioning. Radiographic pictures showed that whole-body were included within the field of irradiation except distal portion of extremities. The rats were irradiated with 1.02 MV gamma rays using cobalt 60 source (Teratron 1000 C, Ontario, Canada) at a dose rate of 125 cGy/minute. Rats in experimental group exposed to single dose of 5-Gy irradiation. A constant distance between radiation source and body surface was 100 cm and radiation field size 23x8 cm. Control animals were subjected to the identical manipulation procedure without irradiation (12,13). Animals were then returned to their cages following exposure and allowed to recover from anesthetic in a quiet, darkened environment.

Blood Obtaining Procedure: Before and on the 10th day after the exposures, all animals were anaesthetized with pentobarbital. Following the anesthesia, blood samples (2cc/100 g body weight) were collected by intracardiac puncture into heparinized tubes. Plasma was separated by centrifuging 4000 rpm for 15 minutes. The levels of MDA in plasma were evaluated by thiobarbituric acid reaction spectrophotometrically described by Yoshioka et. al. (21).

Presentation of Data: The experimental data were analyzed by ANOVA. Wilcoxon matched pairs signed ranks test and Mann Whitney U test were used for statistical analysis. Results are presented as means ± standard deviation of means. Probability (p) values <0.05 were considered statistically significant.

RESULTS

Table 1 shows the initial plasma MDA levels of control and three experimental groups. Before the exposures, mean plasma MDA levels of irradiated, cata-

Table 1: Initial levels of plasma MDA of three experimental groups and control group (mean±standard deviation of mean)

Plasma MDA levels	nmol/ml
1. Irradiated with single dose of 5 Gy	3.5±1.7
2. Catalase-pretreated before irradiation	3.7±1.4
3. Catalase-pretreated before sham exposure	4.0±1.8
4. Sham-irradiated control	3.3±1.6

Table 2.: After all exposures; mean plasma MDA levels of three experimental groups and control group (mean±standard deviation of mean).

Plasma MDA levels	nmol/ml
1. Irradiated with single dose of 5 Gy	30.9±7.2
2. Catalase-pretreated plus irradiated	12.0±4.1
3. Catalase-pretreated before sham exposure	8.9±2.2
4. Sham-irradiated control	8.6±1.8

lase-pretreated plus irradiated and catalase-pretreated plus sham-exposed group did not significantly differ from the values of sham-irradiated controls (Table 1).

The results of our experiments are presented in Table 2. Ten days after the exposures, sham-irradiated controls and catalase-pretreated plus sham-exposed animals showed similar levels of MDA. Ten days after whole-body gamma-irradiation, the mean MDA level was about 3.5 times higher than the mean value of controls (Fig. 1).

Administration of catalase before irradiation markedly reduced the MDA levels in plasma compared to the irradiated rats, indicating a protective effect against lipid peroxidation process (Fig. 2).

DISCUSSION

We detected significantly higher MDA levels in plasma of gamma-irradiated rats compared to the sham-irradiated controls on the10th day after the exposures. These findings showed that high dose of gamma-irradiation could cause lipid peroxidation. However we observed significant increases in plasma MDA concentration in sham-irradiated control animals on the10th day after the exposures It was considered that these changes might be due to blood loss and/or the late effects of anesthesia. Because, this procedure resulted in serious blood loss in rats since the collected blood was approximately 30% of total blood volume.

Siams et al. also observed that rats exposed to single high dose of gamma-rays exhibited an elevated thiobarbituric acid-reactive substance level in serum (13). Rejholcovâ et al. considered that radiation-induced damage was mediated by free radicals and malondialdehyde, one of the major aldehyde products of lipid peroxidation was formed after irradiation in vivo (13). However, It is still controversial whether lipid peroxidation is a cause or consequence of tissue damage (3). Przybyszewski et al. suggested that the increase in lipid peroxide level is used as an early indicator of tissue damage after gamma-irradiation. They demonstrated that administration of the antioxidants, such as vitamin E diminished the level of lipid peroxide in serum of irradiated rats (12). As a consequence of peroxidation of biological membranes and plasma lipoproteins,

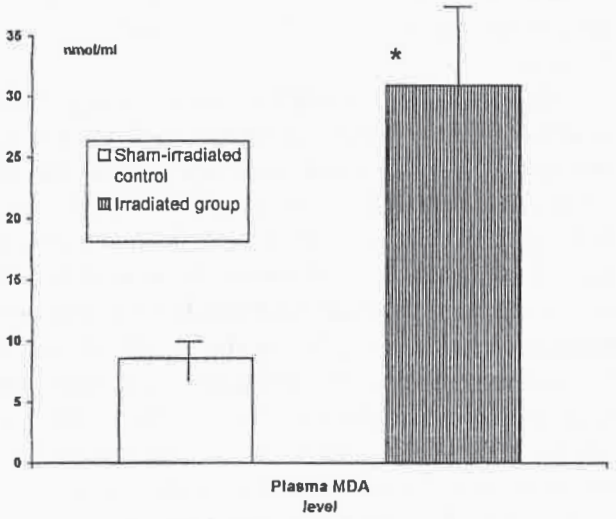

Fig. 1. The comparison of the mean latter plasma MDA levels of control and irradiated rats (*: p<0.05).

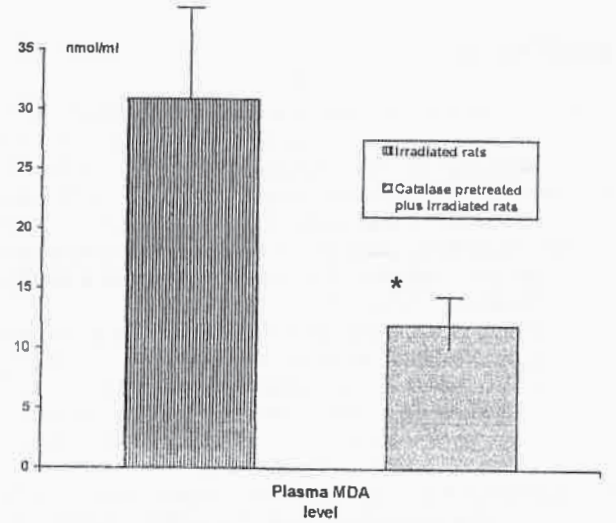

Fig. 2. The mean latter plasma MDA levels of irradiated and catalase pretreated plus irradiated rats (*: p<0.05).

the relatively long-lived aldehydes could be exhausted and they could be involved in pathophysiological effects of high doses of ionizing irradiation (12,19).

We detected high levels of plasma MDA on the 10th post-irradiation day. This finding revealed that lipid peroxidation caused by free radicals was not only formed during irradiation but generated post-irradiation period, as well. In addition, our data indicated that pretreatment of catalase before irradiation markedly reduced the MDA levels in plasma compared to the irradiated rats. In the present experiment, the diminished MDA levels in plasma obtained from the rats pretreated with catalase before irradiation showed that antioxidant therapy could protect the plasma lipoproteins and membrane lipids in tissues against peroxidative damage.

Thiobarbituric acid (TBA) is one of the oldest and most frequently used test for measuring the peroxidation of fatty acids in membranes, lipoproteins and food products. In the TBA test, two moles of TBA reacted with one mole of MDA. Free malondialdehyde is formed during the peroxidation of the most of membrane systems. Malondialdehyde has been widely used to measure "lipid peroxides" in plasma or tissue samples in several diseases (6). Rejhocova et al. suggested that since the bulk lipid stored in fat cells is mostly saturated and therefore not sensitive to lipid peroxidation. Therefore, it is believed that the peroxidative damage induced by irradiation might be originated primarily from the cellular membranes (13). Bienvenu reported that lipid peroxides were also produced by irradiation in various mice tissues (20). In whole-body gamma-irradiation rats, lipid peroxidation which is the most often evaluated by malondialdehyde determination, particularly increased primarily in the radiosensitive tissues (20,22-24). Niehaus et al. hypothesized that O_2^- could diffuse through the membranes and accumulate in their apolar regions. They mediated deesterification of fatty acids which were released from the cell membranes. The release of non-esterified fatty acids to extracellular compartment could at least partially result from reactions of O_2^- (2). We thought that the significant elevation of lipid peroxides in plasma may indicate that one of the target for irradiation toxicity is at least partly plasma lipoproteins. Therefore, one can comment that lipid peroxidation products measured in plasma may originate not only from tissues but also from plasma lipoproteins. However, more detailed researches are needed to determine of the main targets of plasma lipid peroxidation products.

In conclusion, our data indicated that the ionizing irradiation of whole-body induced the peroxidative changes of unsaturated fatty acids containing structures which can be measured as an increment of MDA in plasma. Catalase, one of the most potent physiological antioxidant administered before irradiation, exerted ameliorative effect expressed by diminution of MDA. If this situation exists in clinical conditions during radiotherapy, it is possible that such peroxidizing effects may be limited by the use of suitable amounts of pharmacological and/or dietary antioxidants. Further studies concerning the possible protective effects of other antioxidants on irradiation-induced oxidative injury should be conducted in vivo.

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FINE NEEDLE ASPIRATION OF CAROTID BODY TUMOR

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SUMMARY

Carotid body tumors, (non-chromatin paragangliomas, chemodectomas) are rare tumors. Although uncommon, these neoplasm's should always be considered in the differential diagnosis of a neck mass. Few cases have been reported in the aspiration cytology literature. Fine needle aspiration biopsy smears from six cases of histologically verified carotid body tumor were reviewed. The fine needle aspirates in all cases were similar; abundant cells with round or oval nuclei and marked anisokaryosis with a tendency to form acini or follicular structures. Though the vascularity may vary in different parts of the tumor, there is as a rule a rich network of blood vessels surrounding islets of tumor cells take part.

***Key Words**: Carotid body tumor, Fine needle aspiration Biopsy, Paraganglioma*

Carotid body tumor (CBT) constitute the most common and important group of extra-adrenal paragangliomas (1,2). Paraganglioma is originating from neural crest paraganglion cells and arising at the carotid artery bifurcation or glomus jugulare (2). These tumors, which usually appears as a firm ovoid mass in front of the sternocleidomastoid muscle (3,4). About 10 % of these tumors have behaved in a malignant fashion. This may be manifested as local invasion or metastatic spread, particularly to lymph nodes and lung (1).

In order to investigate the feasibility of differential diagnosis between carotid body tumor and metastatic adenocarcinoma on cytological smears, we have reviewed the biopsy aspirates prepared from six histologically verified carotid body tumors.

MATERIALS AND METHODS

Aspiration biopsy sies of six patients of carotid body tumor which were diagnosed at the at Department of Clinical Cytology during the years 1988 through 1997 were reviewed. All the patients had a neck mass onclinical impressi on. Twoof th e aspiration materials were from Ear-Nos e and Throat Clinic, one from General Surgery Clinic of our faculty hospital. Two of the remaining three materials were from outside of Ankara and one from Numune Hospital. All data were obtained from our Cytology Department registrations. The aspirates consisted of a drop of blood in most cases which contained macroscopically detectable tissue fragments on the smears. The smears were air-dried and stained by May-Grünwald-Giemsa (MGG) stain.

RESULTS

Our patients were five woman and one man. Their average age was 33 (28 to 35 years). All of the cases were with a neck mass. In four patients tumor was located at the bifurcation of the right carotid artery and the other tumors were located at the left of neck. Three of the cases were tough to be as metastatic lymph node by physicians. Only in one case the diagnosis was carotid body tumor and carotid artery angiography was done but was not typical. In the remaining two cases lymph node hyperplasia was suggested by the clinical examination.

Cytomorph ologic findings of the six cases are presented in Table 1.

* This work was presented at the XIIIth National Pathology Symposium, Mersin, Turkey, 24-27 April 1997

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Table 1: Cytomorphologic features of Carotid Body Tumor

Case no	Background	Cellularity	Architecture	Anisocytosis	Cytoplasm	Nuclear shape
1	Bloody	Abundant	Loose group>single cells	Prominent	Abundant+ Grandules	Round or oval
2	Bloody	Abundant	Lose group>single cells	Prominent+ Huge nuclei	Abundant	Round or oval
3	Bloody	Abundant	Cohesive groups	Prominent+ Huge nuclei	Moderate	Oval and spindle
4	Bloody+ HLM*	Scantly	Loose group<single cells	Moderate	Abundant+ Granules	Spindle
5	Bloody	Abundant	Loose group>single cells	Moderate	Abundant+ Granules	Oval and spindle
6	Bloody	Abundant	Loose group<single cells	Prominent	Moderate	Round or oval

* Hemosiderin laden macrophage

The cytological preparations were bloody. There were a lot of hemosiderin laden macrophages in one case. Microscopic review showed fairly numerous tumor cells in five cases and scanty cells in one case. In two cases contain loose groups predominated over single cells, whereas single cells predominated in two cases. Occasionally single cells devoid of cytoplasm (naked nuclei) were observed. In four of the six cases of carotid tumor, areas were found in the smears where the cells were arranged in acinous or follicular structures. One of the cases showed only highly cohesive group of cells. This structures suggested the erroneous suspicion of metastasis of thyroid carcinoma

The tumor cells had abundant cytoplasm and indistinct cellular borders (Fig 1). In three cases the cytoplasm contained variable amounts of granules which took on a reddish tinge with May-Grünwald-Giemsa stain.

Pronounced anisonucleosis was present in all six cases and in two of them huge nuclei were present (Fig 2). The nuclei were usually round or ovoid, but could be of spindle or crescent shape. One case had a majority of spindle shaped cells (Fig 3).

Endothelial cells were seen in all of the cases.

DISCUSSION

A middle age patient with an otherwise asymptotic palpable neck mass is the typical patient (5). The clinical appearance of a CBT is that of a smooth nodular, swelling of varying size lying beneath the anterior

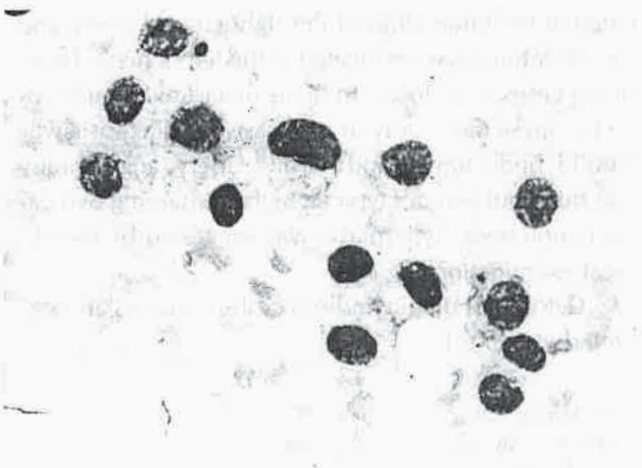

Fig. 1: Aspiration biopsy smear from carotid body tumor. They had abundant cytoplasm (MGG X400).

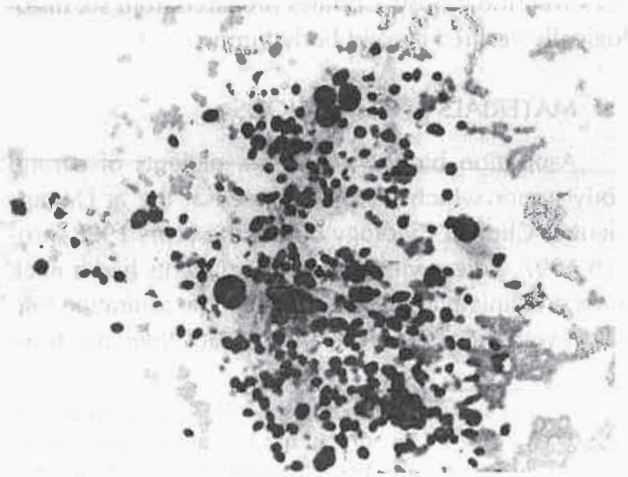

Fig. 2: Pronounced anisonucleosis and huge nuclei in carotic body tumor (MGG X 200).

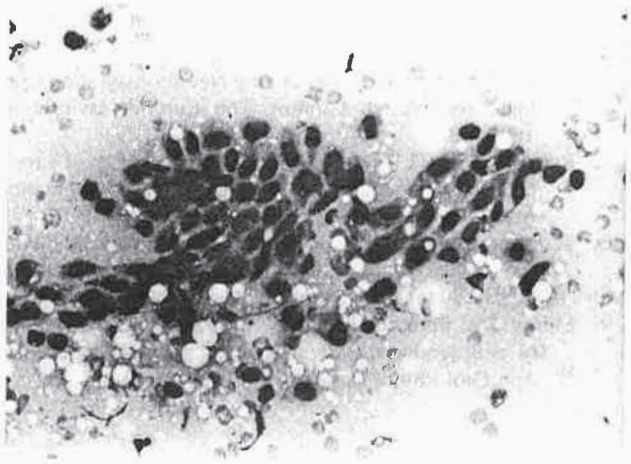

Fig. 3: Spindle shaped tumor cells in this field are fom case 4 (MGG X 200).

part of the sternomastoid muscle and below the mandibular angle (1-6). Because of the tumor's intimate relation to the carotid arteries, the arterial pulsation generally are transmitted through it and may be felt on palpation the swelling (5).

On physical examination, it is a tumor that is mobile horizontally but not vertically (3). The most helpful features in the cytological diagnosis of carotid body tumor include the formation of cell clusters, the presence of moderate amounts of pale granular cytoplasm with indistinct borders, and the presence of round to oval nuclei with evenly dispersed chromatin (7). The differential diagnosis should be made mainly with medullar carcinoma of thyroid gland (4-8). The cytological picture of medullar carcinoma varies widely from one case the another. Cells are generally polygonal or fusiform and contain uniform, round or oval nuclei and granular, amphophilic cytoplasm. The cytoplasm sometimes contains granules that stain metachromatically red with the MGG stain (4).

Aspirates from some carotid body tumors contain cells in microadenomatous structures and can be mistaken for metastatic adenocarcinoma (3). Metastasis of thyroid carcinoma was suspected in one case. Morphologic comparison of such slides with aspirate from true metastatic follicular carcinoma of the thyroid, however, clearly reveals the difference. In the latter case the cells are more densely packed and the nuclei are of more uniform size, polymorphism as a rule being absent.

In the neck, CBT may be mistaken for papillary thyroid carcinomas, partly due to the presence of intranuclear cytoplasm inclusions (7).

The differential diagnosis then involves numerous other lesions such as bronchial cyst, lymphadenitis, neurofibromas, neurofibrosarcoma, malignant lymphoma and lymph node metastases from carcinoma or sarcoma above or below the clavicle (3-6).

Immunohistochemistry is important diagnosis of neuroendocrin neoplasm's of the head and neck (9). Follicular carcinoma and papillary carcinoma stain for thyroglobulin. Medullar thyroid carcinoma will stain with calcitonin. But CBT does not stain for thyroglobulin and calcitonin (2,9). In only one case, where material was available for immunohistochemical staining. This case was stained with chromogranin and neuron specific enolase (NSE).

An asymtomatic neck mass should make one consider the diagnosis (6). Aspiration biopsy has there for been recommended for the diagnosis of CBT (3). When this tumor is suspected and transmitted arterial pulsation can be felt, aspiration biopsy must be cautiously contemplated. The reason is the risk of complications due to the rich vascularity of the tumor and its close proximity to the large carotid arteries (1-5). One case of the Engzell' s (3) series illustrate this risk. Local hemorrhage may compress the artery, resulting in a cerebral catastrophe (4). Instead carotid artery angiographing is recommended, which reveals the typical picture of a richly vascularized tumor widening the space between the internal and the external carotid artery. Fine needle aspiration cytology will be done when CBT is not suggested by the clinical examination or if angiography does not indicate this tumor. We have so far not observed any complication.

In conclusion; CBT has distinctive properties that allow an accurate and definitive diagnosis by FNA. The cytomorphologic features have been documented by reexamination of our own series of six cases and by reviewing the cytology literature.

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INCREASED ERYTHROCYTE ANTIOXIDANT ENZYME ACTIVITIES ARE A POSSIBLE PROTECTIVE MECHANISM AGAINST OXIDATIVE STRESS INDUCED BY ACUTE HEMORRHAGE*

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SUMMARY

In this study, the changes in erythrocyte antioxidant enzyme activities and plasma malondialdehyde (MDA) levels induced by serious blood loss were investigated. For this purpose, 2 cc blood/100 g body weight of rats (approximately 30 % of total blood volume) was drawn by intracardiac puncture under light ether anesthesia. Erythrocyte superoxide dismutase (SOD) and catalase activities and level of plasma lipid peroxidation product (MDA) assayed in first blood samples were used as initial values. At the 10th day after acute hemorrhage, blood samples were taken again and measurements of erythrocyte antioxidant enzyme activities and plasma MDA concentration were repeated. Mean plasma MDA level reached a significantly high concentration after blood taken (at 10th day). Mean SOD and catalase activities measured on 10th day after hemorrhage were significantly higher than the initial values in rats. In addition, before and after blood taken (at 10th day), reticulocyte percentage was estimated as approximately 2% and 14% respectively. It was considered that acute hemorrhage followed by increased reticulocyte percentage can depend on high levels of antioxidant enzyme activities in erythrocytes. Therefore, it is concluded that increases in antioxidant enzyme activities may be a protective mechanism against to oxidant stress induced by blood loss.

Key Words: *Hemorrhage, Antioxidants, Oxidants, Free radicals, Lipid peroxidation*

Small concentrations of free radicals are known to originate from normal metabolic reactions, however they are also abundantly generated by various oxidases and intracellular electron transport chains under ischeamic conditions. Cylooxygenases, lipooxygenases, dehydrogenases and peroxidases may also generate free radicals in addition to the autooxidaiton of such compounds as reduced flavins and thiols. Thus due to the subcellular distribution of the enzymes mentioned above, the free radical formation is associated with all of the cell organelles (1-5). High concentrations of free radicals, which are generated by the enzymatic ways such as xanthine oxidase activity from the ischeamic vessel endothelium, can react with many biological molecules (1,2,6-9). On the other hand, erythrocytes possess enzymatic antioxidant systems for protection from harmful effects of reactive oxygen species. Erythrocytes contain Cu-Zn-superoxide dismutase (Cu-Zn-SOD), glutathione peroxidase (GSHPx) and catalase (CAT) activities, being some of the antioxidant enzymes (5,10-13).

In this study the effects of acute and serious blood loss on plasma lipid peroxidation and erythrocyte SOD and catalase activities were examined.

MATERIALS AND METHODS

Animals

The experiments were performed using mature (10-12 week-old) male Wistar rats. Animals were allocated randomly into control (n: 8) and experimental (n: 8) groups. Each rat was housed in individual cage and supplied with standard food and water ad libitum.

Erythrocyte Separation Procedure

Prior to exposure, all rats in experimental group were anesthetized with ether and blood samples

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(2cc/100 g body weight) were collected by intracardiac puncture into heparinized tubes. Plasma and erythrocyte mass were separated by centrifuging 4000 rotation per minute for 15 minutes. This procedure were repeated for biochemical analyses on 10th day following initial blood taking. Control rats were anesthetized with ether but blood samples were not taken. Tenth day measurements of control group were used as control values.

Determination of Erythrocyte Antioxidant Enzyme Activities

The SOD activity of erythrocytes was assayed by the method of Winterbourn et. al. (14). Erythrocyte catalase activity was measured by the method of Aebi (15). SOD and catalase activities were expressed as IU/g Hb and k (sec^{-1})/ g Hb respectively.

Measurement of Plasma MDA Level

Lipid peroxidation product of plasma namely, malondialdehyde (MDA) was measured by thiobarbituric acid reaction using the spectrophotometric method of Yoshioka et. al. (16).

Determination of Reticulocyte Percentage

Reticulocyte percentage were assessed by supravital staining of blood with phosphate buffered brilliant cresyl blue (17).

Statistical Analysis

The results are expressed as mean ± standard deviation of mean. Wilcoxon matched-pairs signed ranks test and Mann-Whitney-U test were used for statistical analysis. Probability (p) values < 0.05 were considered statistically significant.

RESULTS

Following hemorrhage, on the 10th day, plasma MDA levels and erythrocyte SOD and catalase activities increased significantly compared to initial values of rats (Table 1-3). Tenth day values of experimental group were also significantly higher than those of control group. In addition, on the 10th day after blood taking, reticulocyte percentage reached to high levels (Table 4).

DISCUSSION

We observed significant increase in erythrocyte SOD and catalase activities and plasma MDA levels in rats following hemorrhage. Elevated plasma MDA levels indicated that serious hemorrhage induced syste-

Table 1: Erythrocyte SOD activities of control and blood taken rats (Mean±SD)

		Initial Values	10th Day Values	Comparison of Initial and Letter Values
Erythrocyte SOD Activities (U/g Hb)	Experimental Group (n:8)	4002±845	6673±1108	p<0.05
	Control Group (n:8)		4222±325	
Comparison Between Control and Experimental Groups			p<0.05	

Table 2: Erythrocyte Catalase activities of control and blood taken rats (Mean±SD)

		Initial Values	10th Day Values	Comparison of Initial and Letter Values
Erythrocyte Catalase Activities (k/g Hb)	Experimental Group (n:8)	164±71	336±117	p<0.05
	Control Group (n:8)		174±31	
Comparison Between Control and Experimental Groups			p<0.05	

Table 3: Plasma MDA levels of control and blood taken rats (Mean±SD)

		Initial Values	10th Day Values	Comparison of Initial and Letter Values
Plasma MDA levels (nmol/ml)	Experimental Group (n:8)	3.3±1.6	8.6±1.9	p<0.05
	Control Group (n:8)		4.4±2.0	
Comparison Between Control and Experimental Groups			p<0.05	

Table 4: Reticulocyte percentage of control and blood taken rats (Mean±SD)

		Initial Values	10th Day Values	Comparison of Initial and Letter Values
Reticulocyte Percentage (%)	Experimental Group (n:8)	2.0±0.5	14.0±2.2	p<0.05
	Control Group (n:8)		2.1±0.3	
Comparison Between Control and Experimental Groups			p<0.05	

mic oxidative stress in organism. SOD and catalase, which are important components of enzymatic antioxidant defense system, can detoxify oxygen free radical effectively (4,10,18). The findings of our present investigation support our hypothesis that serious acute blood loss increases the resistance of erythrocytes to oxidative stress. In nature, serious hemorrhage induced metabolic changes are similar to that caused by ischemia-reperfusion in tissues. Under hypoxic conditions, xanthine oxidase and enzymatic activities in electron transport chains in cell are the two major sources of free radical production (5-7,11,12, 19,20).

Hemorrhagic shock often causes severe ischemia in various tissues. Structural and functional changes and lesions in mucosal membranes have been reported in man and experimental animals following hemorrhagic shock (6). Severity of mucosal lesions is dependent upon both the duration and severity of ischemia. Catalase provides significant protection against ischeamic injury. Blood loss induced increase in sympathetic activity distorts tissue perfusion in immediate post-hemorrhagic period. In later period, ischemia often induced precapillary sphincter relaxation and increase in vascular permeability. Since increase in capillary permeability is largely prevented by SOD and catalase, it is suggested that free radicals are mainly responsible for vascular permeability increase (16). It was proposed that xanthine oxidase which is well-documented biologic source of oxygen radicals under hypoxic conditions. During the ischeamic period, ATP is catabolized to hypoxanthine. Xanthine oxidase, which is in dehydrogenase form in normal oxygenation state, is converted into oxidase form in hypoxic conditions. Allopurinol, which is a competitive inhibitor of xanthine oxidase, provides protection against tissue injury in hemorrhagic shock (6). Increased permeability results in Ca^{++} influx, which activates calmodulin-regulated intracellular protease. When protease is activated, it becomes another major source of free radicals in the ischeamic tissues. Oxygen radicals may also stimulate leukocyte chemotaxis and release of leukotriens, which causes interstitial edema in ischeamic tissues (6). It was reported that the destructive effects of activated monocyte-derived reactive oxygen metabolites on natural killer cells was prevented by catalase (21).

Yoshioka et al reported that dehydration induced renal hypoperfusion is predisposing factor for free radical mediated renal injury. They showed that SOD

and catalase activities in kidneys of dehydrated rats reduced significantly. Reduced antioxidant enzyme activities of kidneys in dehydrated rats may be related with the abundant generation of reactive oxygen species (22). It was suggested that excessively generated free radicals induced by renal hypoperfusion may lead to inactivation of antioxidant enzymes and/or reduction of antioxidant enzyme synthesis by alteration of enzyme protein transcription.

Adequate free radical scavenging enzymes are available to inactivation of reactive oxygen species in the normal conditions whereas, serious hemorrhage would increase free radical production thereby exceeding the antioxidant capacity of erythrocytes resulting in oxidative stress. Our findings showed that reticulocyte percentage increased significantly on 10th day after hemorrhage in rats. Stimulation of hemopoiesis related with blood loss causes the increase in reticulocyte percentage. The increases in activities of erythrocyte antioxidant enzymes are also possibly due to the new generated erythrocyte mass. It is well known; new enzyme syntheses are not seen in mature erythrocytes because of the absence of endoplasmic reticulum and ribosome. Therefore, it is considered that the highest activities of antioxidant enzymes are present in young erythrocytes and aging possibly decreases their activities. Our data shows that serious blood loss induced increase in lipid peroxidation that is widely accepted as a good indicator of oxidant stress. In the blood taken animals, the substantial induction of antioxidant enzyme activities acquired by blood loss protects that organism against oxidative stress.

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DRUG MISUSE AND POTENTIAL PROBLEMS IN ELDERLY PATIENTS: GENERAL PROPERTIES THE DRUG USE IN OLD AGE

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SUMMARY

Inappropriate drug use is a common problem in older people. Many older patients take their medications incorrectly and large number of patients receive over the counter drugs from the pharmacy. In this study we evaluated general properties of the drug use in a community dwelling. Two hundred twenty five people were assessed by patients' files and local physician's reports. Among them, 189 had various chronic diseases which were diagnosed in several hospitals and 36 had no diagnosed chronic disease. Hypertension (57 patients, 25.3%), neuropsychiatric problems (50 patients, 22.2%), atherosclerotic heart disease (32 patients, 14.2%) were the most common diseases. When the drugs examined, 31% of the consumed drugs were cardiovascular agents, 12.5% was neuropsychiatric drugs and 9.6% was diuretics. Almost 21% of people were not using regular medication, also 25% of the people were receiving one regular medication. Average medication for each patient per day was 3.4. Percentage of the people who takes 3 or more regular medication was 60%. Among them, 29 patients (13%) were taking inappropriate medications which can be dangerous. The most common drug misuse was taking same compounds which have different trade names (10 patients). Average medication in patients who have inappropriate drug use was 5 drugs per day. This study shows that drug misuse is somewhat common problem in older age patients. Therefore, avoiding drug reactions and writing safe prescriptions needs extra care and efforts.

Key Words: *Drug therapy, Elderly patients, Aging, Drug misuse*

It is well known that the people have more various diseases with increasing age. Therefore, elderly people takes more prescripted or non-prescripted drugs than patients in any younger age group. It is shown that the incidence of the adverse reactions were increased with age and using number of drugs. In USA, the elderly people is 12% of the total population but they takes 30% of the total drug prescriptions (1). Physiological changes with aging can effect drug metabolism and elimination. It is reported that nearly one-quarter people in age of 65 and older has been taken potentially dangerous inappropriate medications (2). Two-thirds of patients age 65 or older use one or more drugs daily. The average drug use in this age group is 5 to 12 drugs per day, and fewer than 5% of the older population use no drugs (3). The aim of this study was to investigate general properties of the drug use in elderly people.

PATIENTS AND METHODS

We recruited 225 people living in the biggest community dwelling in Ankara. The general information about the people's diseases and their treatment were evaluated with their follow up files and their local physician's reports. One hundred thirty three of them were male (mean age 72±10) and 92 were female (mean age 74±11), 189 of them had various diseases and remains did not have any diagnosed disease. Some of them were under the routine control of the hospitals. Their medications and examinations and blood tests had been written regularly to the follow up files in the community dwelling.

RESULTS

When we evaluated the patients' files and reports in the community dwelling, as shown on the Table 1,

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Table 1. Disease of the residents in the community dwelling

Diagnosis	Number of Patients	Percentage (%)
Hypertension	57	25.3
Neuropsychiatric problems	50	22.2
ASHD	32	14.2
GI problems	20	8.9
Musculoscletal Problems	17	7.6
COLD	13	5.8
No chronic disease	36	16

ASHD: Atherosclerotic hearth disease, GI: Gastro intestinal, COLD: Chronic Obstructive lung disease

Table 2. Drug groups; taken in the community dwelling

	Percentage (%)
1. Cardiovascular agents	31
2. Neuropsychiatric drugs	12.5
3. Diuretics	9.6
4. Agents for GIS	7.7
5. For COLD	7.2
6. Analgesic agents	6
7. Peripheral vasodilatör	6.8
8. Vitamins	4.8
9. Others	14.4

GIS: Gastrointestinal System COLD: Chronic obstructive lung disease

most of them had hypertension and neuropsychiatric problems (57; 25.3% of patients and 50; 22.2% of patients, respectively). Also, atherosclerotic heart disease was the other common problem in these people (32 patients; 14.2%). When the drugs were evaluated, 31% consumed drugs consist of cardiovascular agents (Table 2). Neuropsychiatric drugs were second (12.5%) and diuretics were third common used drug groups. As shown by Table 4, cardiovascular agents were Ca antagonists, digitalis, angiotensin converting enzymes (ACE) inhibitors and nitrates. Most of the neuropsychiatric drugs were anti-depressants, major tranquilizers, anxiolytics, anti-parkinsonian drugs. The average drug number for each patient was 3.4. Only 48 (21%) of them were not taking regular medication. Almost 60% of people were taking average 3 or more drugs and 25% of people were taking only 1 regular drug in the community dwelling (Table 4). As shown by Table 5, totally 29 (13%) people had inappropriate medication, if the people who uses 3 or more drugs was taken into consideration, this would be 26%. The most common inappropriate drug use was the taking same compound which have different trade names (ACE inhibitors, Ca antagonists, bronchodilators, anticoagulant drugs). Furthermore, digitalis and K loosing diuretics, ACE inhibitors and K sparing diuretics were also potential dangerous combinations that need careful regular blood test. The other dangerous drug interactions we found were prescribing of the two drug that have opposite effect (negative inotropic and positive inotropic agents in patients with congestive heart failure) and prescribing nonsteroidal antiinflammatory drugs (NSAID) in patients with dyspepsia and peptic ulcer. The average drug number for patient who had inappropriate medication was 5 drug per day. Taking NSAID was somewhat common particularly over the counter (about 86 patients (38%) were taking NSAID irregularly) but regular use was only 6%. Therefore, side effects and potential drug interaction with NSAID could be more than documented and expected adverse reactions.

Table 3. Average number of drugs for per patient.

Number of drugs	Percentage (%)
1	25
2	14.8
3	18.2
4	16.0
5	13.8
6	5.8
7-8-9	6.4

Table 4. Percentage of different cardiovascular agents; using i the community dwelling

Drugs	Percentage (%)
1. Ca Antagonists	20.8
2. Digoxin	19.3
3. ACE inhibitors	19.3
4. Nitrates	18.4
5. Anti-thrombotic agents	17.6
6. Alpha and Beta blockers	4.6

ACE: Angiotensin converting enzymes

Table 5. Drug interactions that can be potential problems f adverse interaction

	Number of Patients
Drugs, same compound but different trade name	10
Peptic ucler, dyspepsia and NSAID	6
K sparing diuretic and ACE inhibitor	5
Congestive heart failure and negative inotropic agents	4
Digoxin and K loosing diuretic	3
Oral anti-diabetic drug in chronic renal failure	1

NSAID: Non steroidal antiinflammatory drugs, A Angiotensin converting enzyme inhibitors.

DISCUSSION

It was reported that the number of drugs taken by older patients increases the adverse drug interaction and reaction (1). When two or more drugs are taken the potential for interaction is 6%, but the risk increases to 50% with five drugs and to 100% with eight drugs. Since the drug induced illness are so difficult to diagnose and often go undetected for long time, it should be considered in any unexplained clinical situation (4). In a study, it was shown that physicians prescribe potentially dangerous inappropriate medications for nearly one-quarter (23%) of all Americans age 65 and older (2).

In our study, we found that 29 (13%) patients were taking inappropriate medication in community dwelling. The most common inappropriate drug use (5%) was receiving two same compound which have different trade name. If the people who did not take regular medication (21%) and take only one medication (25%) disregarded and only people who take 2 or more drugs were taken into consideration, this percentage would be higher. The patients with inappropriate medication were using average 5 drugs per day. It shows that polypharmacy is a common and potential dangerous problem in elderly people. It can be caused by patient and physician factors. Patient factors are that the older patients self medicate with over the counter drugs more frequently than the general adult population. It is also quite common in elderly people to share their drugs with other people. On the other hand, overprescription is another important aspect of the problem. Some physicians tend to prescribe more drugs for the elderly people to satisfy them.

Our study also shows that drug-drug interaction increases with the number of drugs. This can be result from lack of enough cooperation between doctors and patients. Elderly patients are more likely to have two prescriptions for their diseases from different physicians. When the patients take many drugs, they get confused about the medications and they take their medications incorrectly which also increases the risk of adverse reactions. Besides, noncompliance to the therapy is a very important cause of drug misuse in elderly people.

In most elderly patients, the dosages of the drugs were not arranged on grounds of age and renal functions, routine adult doses were used. This does not means elderly people must use very low dose of drugs, it means, these patients should be prescribed lower doses as a starting dosage and it should be gradually increased on the basis of renal functions and age related changes on the drug metabolism (10).

Our study shows that drug overuse can cause dangerous potential adverse drug reactions. These important reactions can be divided as; drug-drug reactions, drug-disease reactions, drug-alcohol reactions, drug-nutrient reactions (5). All reactions must be considered when the prescriptions are written for elderly patients. We found that 10 patients were using two same compounds with different trade names, 4 patients were using two drugs that have opposite effect, 5 patients were using K sparing diuretic and ACE inhibitors, 3 patients were using K loosing diuretic and digitalis which are good examples to the drug-drug reactions. Also, the negative inotropic medication that was prescribed for congestive heart failure (4 patients), NSAI drugs in patients with dyspepsia and peptic ulcer (6 patients) and oral antidiabetic drug (biguanid) in patient with chronic renal failure (one patient) are the examples of the drug-disease interactions. Taken together, we found 29 patients (13%) with inappropriate drug use in the community dwelling.

Aging, along with physiological changes like renal functional, hepatic, body composition and GI changes are responsible for the most adverse drug reactions (7,8,9). All these alterations can effect the drug metabolism in the several stages of drug metabolism like absorption, distribution, protein binding, biotransformation and excretion.

In our group of patients NSAID seems to be less taken than expected. But we reported only patients who were taken regular NSAID. Therefore, it was underestimated together with antacid drugs and other possible over the counter drugs.

Taken together, it need to be underlined some important points.

- Older patients respond to drug doses that are lower than are used in younger people. So it must be general rule for the geriatric prescriptions that start low and go slow.
- Prescribe the fewest number of drugs possible.
- Periodically review the patient's medications, and get rid of any unneeded or duplicated drugs.
- Became aware of the price of the medications.

As a result, because of the widespread practise of polypharmacy in the elderly plus physiological changes with aging, there is an increased potential for drug interactions. To avoid drug reactions, all considerations must be remembered and tried to write the safest prescriptions.

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PLASMA FERRITIN LEVELS IN ACUTE MYOCARDIAL INFARCTION

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SUMMARY

Free iron catalyzes free radical production, which generates a range of potent oxidants that can induce oxidation of lipids. As serum ferritin partially reflects the iron stores in the body, high ferritin level is postulated to reflect a state of increased free radical generation. Our study suggested that high ferritin levels must be atherogenic and possibly explain partially the sex difference in the incidence of Ischemic Heart Disease (IHD).

In this study Iron Binding Capacity (IBC), ferritin and serum iron levels in 53 patients (40 male, 13 female) with Acute Myocardial Infarction (AMI) are compared to those found in the control group (n=24; 12 male, 12 female). The site of AMI was anterior wall in 34 and inferior wall in 19 patients (Forty of the patients and twelve of the control group were male). The results of the two groups are compared according to sex. The serum feritin levels of forty male patients with AMI were higher than those of male controls ($p<0.001$). In male patients with AMI serum IBC was lower than those of male controls. The difference was not statistically significant ($p>0.05$). In female patients with AMI serum iron and ferritin levels were higher than those of female controls. This was not also statistically significant ($p>0.05$).

In female patients serum IBC was lower than the control group and the difference was statistically significant ($p<0.01$). Coronary Angiography (CAG) was performed in 46 of these patients and "Multiple Vessel Disease" (MVD) (Odds ratio=5) and Congestive Heart Failure (CHF) (Odds ratio=3.3) were seen more in patients who have high ferritin levels.

Conclusion: This study suggests that high ferritin levels should be appreciated atherogenic and possibly explain partially the sex differences in the incidence of IHD.

Key Words: *Serum Iron, Iron Binding Capacity, Ferritin, Myocardial Infarction*

Oxygen free medicals promote the oxidation of lipids, which have been postulated to be involved in the development of athoresclerosis (1). This is supported by the observed association between the titer of autoantibodies against oxidatively modified Low Density Lipoprotein (LDL) and the progression of carotid atherosclerosis in men (2). In concordance with this theory, the levels of antioxidant vitamins, especially E, have been shown to be inversely relate to the incidence of ischemic heart disease (3-6). In a recent study by Salonen et al, the level of serum ferritin was suggested to be an independent risk factor for coronary heart disease (7).

Free iron catalyzes free radical production, which generates a range of potent oxidants that can induce oxidation of lipids. Free radical production and lipid peroxidation could be prevented by the iron-chaleting agent desferrooxamin (8-11). The relation of high iron stores and coronary heart disease was first suggested by Sullivan, to explain the heart disease risk in sex differences (12). Premenopausal, women have much lower iron stores than men of the same age because of regular blood loss through menstruation.

In most of the previous studies the three parameters of iron metabolism, serum ferritin, TIBC and iron were not studied all together.

In this study we have calculated the established major risk factors for CHD including Total Serum Cholesterol (-CHL), High Density Lipoprotein Cholesterol (HDL-CHL) Triglycerides (TG), Blood Pressure (BP),

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Smoking, Serum ferritin levels, TIBC and iron levels in 53 patient during AMI.

METHODS

53 patients, (40 men, 13 women) who are admitted to Ankara University Medical Faculty, Cardiology Department with AMI, are included in this study. 34 of these patients had anterior wall and 19 inferior wall AMI. Mean age for men were 57.8±13.9 years and for women 63.4±8.8 years. In this study 24 healthy persons (12 men, 12 women) were taken as the control group. The mean age for control group were between 22-58 (men 36±8, women 29±7). After a fasting period of 12 hours, blood samples were taken from the patients for serum iron, ferritin levels and TIBC in the admittance of 12 and 48 hours of AMI. Serum iron and TIBC is established by using Pointe Scientific Kit. Ferritin level is established in Endocrinology laboratory by chemiluminescent immunometric method. Normal ferritin levels are accepted for men 19-370 ng/ml and for women 9-120 ng/ml.

Because Serum Iron, IBC and ferritin levels for men and women are changeable these values are compared in patients of the same gender.

Total cholesterol was determined by a chemical colorimetic method and TC fluorometrically. HDL-CHL was determined by the heparin manganese method. The other risk factors of the patients (Hypertension in the story, Diabetes Mellitus, Smoking, Family history) are searched. One month later after AMI, stress test is performed to the patients. Coronary Angiography is performed to 46 patients who had abnormal stress test and still had angina in spite of medical treatment.

Mann-Whitney U test is established to asses the statistical outcomes. Odds ratio is calculated for male and female patients in evaluating Hypertension (HT), Diabetes Mellitus (DM), family history and smoking.

RESULTS

Clinical significance of the patients and laboratory findings are shown in Table 1. Serum ferritin levels in male patients with AMI were 232.97±175.17 ng/ml and 62.20±37.39 ng/ml in male controls. This difference was found very important statistically ($p<0.001$) (Table 2). Serum ferritin levels in female patients with AMI were 101.53±85.81 ng/ml and 55.70±21.20ng/ml in female controls ($p>0.05$). When

Table 1: Clinical significance of the patients and laboratory findigs

	Men n=40	Women n=13	Odds Ratio	P value
Age	55.55±12.97	62.61±8.8		
HT	8	3	13.3	
DM	6	3	1.7	
Smoking	27	1	24.9	
Family History	9	3	1.03	
Systolic B.P.	113.75	133.84		
Diastolic B.P.	75	82.30		
HF	24	4	3.34	
MVD	21	2	5	p<0.05
Tot. Chol.	203.32±49.95	219.53±39.55		NS
HDL-Chol.	37.27±9.12	33.61±11.36		NS
LDL-Chol.	159.70±25.65	126.70±32.46		p<0.01
TG	148.82±61.65			

NS: Not Significant, HT: Hypertension, DM: Diabetes Mellitus, B.P.: Blood Pressure, HF: Heart Failure, MVD: Multiple Vessel Disease, Chol: Cholesterol, TG: Triglyceride

Coronary Angiography is performed to 36 male and 10 female patients.

Table 2: Serum iron, ferritin levels and total iron binding capacity (TIBC) in the study group and controls.

	Men n=40	Control n=10	P value	Women n=13	Control n=10	P Value
Serum Iron	99.67±51.16	71.30±11.97	N.S.	96.53±31.14	75.60±11.53	N.S.
Serrum Ferritin	232.97±175.17	62.20±37.39	p<0.001	101.53±85.81	55.70±21.20	N.S.
TIBC	148.17±56.72	170.10±56.31	NS	175.53±61.61	282.60±82.82	p<0.01

ferritin levels of male and female patients are compared, ferritin levels of males found higher ($p<0.01$). Serum iron level in male patients with AMI were 99.67±51.16 mg/d1 and 71.30±11.97 mg/dl in male controls. This difference was meaningless statistically ($p>0.05$). Serum iron level in female patients with AMI was 96.53±31.14 mg/dl and higher comparing to the female controls (75.60±11.53 mg/dl) also was not significant statistically ($p>0.05$).

In male patients with AMI ITBC was 148.17±56.72 mg/dl and 170.10±56.31 mg/dl in control group ($p>0.05$).

In female patients TIBC was 175.53±61.61 mg/dl and in female controls 282.60±82.82 mg/dl ($p<0.01$) (Table 2).

When the other risk factors are searched, HT and DM were found more in female patients (odds ratio 13.3 and 1.7), smoking and family history in male patients (odds ratio 24.9 and 1.03). T-CHL, HDL-CHL and TG levels were very similar in genders and showed no significant difference. But LDL was higher in male patients ($p<0.01$). During the clinical follow-up Sysolic and Diastolic BP was found higher in male patients (113.75 mmHg versus 133.84 mmHg. and 75 mmHg versus 82.30 mmHg). CHF was found more in males (odds ratio 3.34). In CAG multivessel disease was more in male patients ($p<0.05$).

DISCUSSION

In some recent studies serum ferritin level was suggested to be an independent risk factor for CHD (7,8,12,16). Free iron catalyzes the generation of free radicals as serum ferritin partially reflects. The iron stores in the body, high ferritin was postulated to reflect a state of increased free radical generation (8).

Free iron catalyzes free radical production which generates a range of potent oxidants that can incude oxidation of lipids (8-11). The oxidation of LDL is thought to occur mostly in the subendothelial layer of the arteries prone to atherosclerosis (17). Atherosletoric lesion have recently been shown to be rich in both iron and copper and the crater from these lesion was found to induce lipid peroxidation that was inhibited by the iron chelater desforrioxamine (12,18-21).

The association of high iron stores and CHD was first suggested by Sullivan JL to explain the gender differences (12).

Premenopausal women have much lower iron stores than men of the same age because of regular blood loss during menstruation period (21).

In the previous studies Serum Iron and TIBC was calculated but ferritin was not. Preliminary results have been published regarding the role of iron parameteres in CHD in the United States by Stampfer and coworkers (14). They did'nt detect any correlation between ferritin and risk of Myocardial Infarction (MI). In the most of previous studies the three parameters in iron metabolism (iron, TIBC and ferritin) were not evaluated together. Different results are established in the later studies. Some of the authors had found relation between AMI and serum ferritin level (7,8,12,16) but some not (6,13,14,15).

In our study serum ferritin level is found in male patients with AMI twice comparing to the female ones ($p<0.01$). Because the ferritin level differs in male and female patients, the levels are compared between male patients and male controls, female patients and female controls.

We have found serum ferritin level high in male patients with AMI comparing to the male controls ($p<0.001$).

Fuchs D and coworkers had concluded that high stored iron levels as assessed by elevated serum ferritin may result from chronic inflammatory processes (22). But it is unlikely that the observed association between serum ferritin concentration and the risk of AMI would have been produced by the dependence of serum ferritin on inflammation or an macrophage activation (12,13,23).

When the serum iron levels of male and female patients with AMI was compared to the control group the result was not significant (NS).

The serum iron binding capacity might be a more reliable predictor of this accumulation of free iron in the vessel wall than the total iron in the vessel and Liao found no relation between TIBC and the incidence of MI (24).

In our study TIBC levels showed no significance between male patients with AMI and male controls, but was lower in female patients comparing to the female controls ($p<0.01$). So we suggest that TIBC is valuable comparing to serum iron in AMI.

When the other risk factors are considered we observed DM and HT more in female patients (odds ratio 1.3 and 13.3). We also found that smoking was more in male patients comparing to female ones (odds ratio 24.9). In some studies it is concluded that ferritin increasses LDL oxidation (18-21). We have found in our study LDL high in male patients comparing to females ($p<0.01$). CAG is performed to 36 male and 10 female

patients who had abnormal stress test and who still had post MI angina. We observed multivessel disease ($p<0.05$) and CHF more in male patients (oss ratio= 3.3).

We suggest that high levels of ferritin increases the LDL Cholesterol oxidation and could be a risk factor for AMI.

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LOW SENSITIVITY OF THE ELECTROCARDIOGRAM IN DIAGNOSIS OF HYPERTENSIVE LEFT VENTRICULAR HYPERTROPHY

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SUMMARY

Clinical recognition of hypertensive cardiac involvement depends primarily on the use of noninvasive methods. Although electrocardiography is the usual method of identifying left ventricular hypertrophy on routine evaluations, the electrocardiogram detects only a small percentage of the instances of left ventricular hypertrophy that are documented by echocardiograms. This study investigated the diagnostic accuracy of Romhilt-Estes criteria in diagnosing left ventricular hypertrophy in hypertensive patients and to assess the impact of age, sex, blood pressure level, and patterns of left ventricular geometry on the diagnostic accuracy of electrocardiography for detecting left ventricular hypertrophy. Of the 169 hypertensive subjects, electrocardiographic left ventricular hypertrophy was present in 26 (15 %). The overall sensitivity of the Romhilt - Estes criteria in the diagnosis of left ventricular hypertrophy was 26%, spesificity was 96% and overall diagnostic accuracy was 55%. In conclusion, we found that the sensitivity of electrocardiography for left ventricular hypertrophy was low, even when blood pressure level, age, sex, and patterns of left ventricular geometry were taken into consideration.

Key Words: *Echocardiography, Electrocardiography, Hypertension, Left ventricular hypertrophy*

Because of its low cost and broad availability, electrocardiography (ECG) is currently recommended as the routine test to detect left ventricular hypertrophy (LVH) in all subjects with high blood pressure (1). Its major disadvantage is its low sensitivity; it identified LVH in only a small percentage of patients with mild to moderate hypertension who showed evidence of probable or definite LVH on echocardiography (2- 5). Despite this, the presence of electrocardiographic LVH has been associated with a twofold increase in mortality from cardiovascular disease over that resulting from hypertension alone (6). The purpose of this study was to determine the diagnostic accuracy of Romhilt-Estes criteria in diagnosing LVH in hypertensive patients and to assess the impact of age, sex, blood pressure level, and patterns of left ventricular geometry on the diagnostic accuracy of ECG for detecting LVH.

METHODS

Data were obtained from 169 patients with borderline to severe essential hypertension and 40 normal subjects. The study population consisted of 169 patient with essential hypertension who were referred 2 dimensional and Doppler echocardiographic studies at our institute between July to December 1995. The eligibility criteria were as follows: no evidence of secondary causes of hypertension; no evidence of diabetes mellitus; no history or physical or electrocardiographic signs of valvular, primary myocardial, or coronary artery disease; no previous treatment with digitalis. In addition, subjects with complete bundle branch block, atrial fibrillation, and Wolff-Parkinson- White syndrome were excluded from the analysis. There were 106 women and 63 men, ranging in age from 23 to 80 years (mean ± SD 55 ± 10).

Blood pressure measurement used in the study were taken with a mercury sphygmomanometer at the time of echocardiography with the patient supine.

ECG were recorded using commercially available a standart machine. All ECG were read according to the Romhilt - Estes criteria (7) by two independent investigators (Romhilt-Estes point score ≥4).

Echocardiographic examinations were performed using a Toshiba 140 A recorder with a 3.75 MHz

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Table 1: Sensitivity, specificity and overall diagnostic accuracy of electrocardiographic Romhilt-Estes criteria in the diagnosis of left ventricular hypertrophy

	Age (years)			Sex		Diastolic blood pressure (mmHg)			Systolic blood pressure (mmHg)		
	All patients (n=169)	<55 (n=66)	≥55 (n=103)	Women (106)	Male (n=63)	90-104 (n=107)	105-114 (n=25)	≥115 (n=37)	140-159 (n=33)	160-179 (n=56)	≥180 (n=80)
Sensitivity	26	32	24	17	38*	15	14	8	20	12	25
Specificity	96	97	98	98	92	93	100	92	100	100	90
Overall diagnostic accuracy	55	64	58	58	60	36	52	32	64	59	50

Values are expressed as%. * p<0.01 versus vomen.

transducer. Measurements were taken at or just below the tip of the mitral valve. Left ventricular internal dimension and septal and posterior wall thicknesses were measured at end- diastole and end- systole, according to the American Society of Echocardiography guidelines (8). Left ventricular mass was calculated using Reicheck and Devereux formula (9):

Left ventricular mass (g)= 1.04 [(LVID +PWT + IVST) 3 - (LVID) 3] - 13.6 where LVID is the left ventricular diastolic diameter, PWT the posterior wall thickness and IVST the interventricular septum thickness. This calculation was corrected for body surface area (left ventricular mass index). Relative wall thickness was measured at end diastole as the ratio of 2x (posterior wall thickness / internal dimensions). Patterns of left ventricular anatomic adaptation to hypertension were identified by categorizing patients according to values of left ventricular mass index and relative wall thickness. The echocardiographic criterion of left ventricular hypertrophy was a left ventricular mass index ≥110g/m² (female) and ≥134g/m² (male) (10). A partition value of 0.45 relative wall thickness was used for both men and women. Four different patterns of left ventricular anatomic adaptation to hypertension were identified by categorizing patients according to values of relative wall thickness and left ventricular mass index (11). Elevated relative wall thickness with increased mass index identified the presence of concentric as opposed to eccentric hypertrophy and in the presence of normal left ventricular mass identified concentric left ventricular remodeling.

RESULTS

There were 90 (53%) patients with echocardiographic left ventricular hypertrophy, 53 women, 37 men. Of the 169 hypertensive subjects, electrocardiographic left ventricular hypertrophy was present in 26 (15 %). The overall sensitivity of the Romhilt - Estes criteria in the diagnosis of left ventricular hypertrophy was 26%, spesificity was 96% and overall diagnostic accuracy was 55% (Table 1). When patients were subdivided according to age, sex and blood pressure levels, no significant differences were found except for men. The sensitivity of ECG were higher in men than in women. Among hypertensive patients, left ventricular mass index and relative wall thickness were normal in 25%, whereas 41% had concentric hypertrophy (increase in both variables), 22% had increased relative wall thickness with normal ventricular mass ("concentric remodeling") and only 12% had increased mass with normal relative wall thickness (eccentric hypertrophy). Of the 69 patients with concentric left ventricular hypertrophy, electrocardiographic left ventricular hypertrophy was present in 20, whereas in 21 patients with eccentric left ventricular hypertrophy, electrocardiographic left ventricular hypertrophy was present in 3.

Of the 40 normal subjects, only one patients had electrocardiographic left ventricular hypertrophy (Romhilt -Estes point score is equal 4), but had no echocardiographic LVH.

DISCUSSION

Several epidemiologic studies have demonstrated that left ventricular hypertrophy is an independent and important risk factor (12-15). A large number of studies concerning the relation between electrocardiography and left ventricular mass have been published in the literature. Before the introduction of echocardiographic studies, Romhilt-Estes criteria were determined at autopsy to be the most accurate in diagnosing left ventricular hypertrophy (7). Many echocardiographic studies have found electrocardiographic criteria to have low sensitivity (16-20%), although specificity (>90%) is resonable (16). In this study, we used Romhilt-Estes criteria for diagnosis of left ventricular hypertrophy. In 169 patients studied at our institution, sensitivity of the Romhilt -Estes criteia for left ventricular hypertrophy was 26%, specificity was 96%, and overall diagnostic accuracy was 55%. Neither age nor blood pressure level affected the ability of electrocardiogram to diagnose of left ventricular hypertrophy. The sensitivity of electrocardiography for left ventricular hypertrophy were higher in men than in women (38% vs 17%, $p<0.01$). Similarly, in another study which uses Minnesota voltage criteria, it was concluded that the spesificity and sensitivity of ECG in determination of LVH was lower in females than in males (17). The ability of electrocardiogram to detect of left ventricular hypertrophy was higher in patients with concentric hypertrophy than in patients with eccentric hypertrophy (sensitivity 29% vs 14%, $p>0.05$).

In conclusion, we found that the sensitivity of electrocardiography for left ventricular hypertrophy was low, even when blood pressure level, age, sex, and patterns of left ventricular geometry were taken into consideration. Despite prediction of left ventricular mass from the electrocardiography may offer a low cost alternative, echocardiographic determination of left ventricular mass remains the method of choice in most clinical settings.

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HIGH DOSE INTRAVENOUS IMMUNOGLOBULIN (IVIG) TREATMENT IN PATIENTS WITH LUPUS NEPHRITIS

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SUMMARY

High dose intravenous immunoglobulins (IVIG) have become an important treatment modality for some immune mediated diseases. We investigated the effect of high dose IVIG in systemic lupus erythematosus (SLE).

Eight patients with active renal involvement disease (all of them female, mean age; 25.8 ± 8.1, mean disease duration; 30.5 ± 16.1 months) were given 400 mg /kg /day 4. generation IVIG preparation (Octagam. Octapharma, Pharmazeutika Wien, Austria) during the days 1 to 5 and 21 to 25. Overall disease activity was measured by the SLAM score. The measured systemic lupus activity was declined from 19.0 to 4.38 ($p<0.001$). After initiation of therapy a decline in ds DNA antibodies and proteinuria was observed in most patients ($p<0.05$, $p<0.05$ respectively). Complemant 3 protein was increased, where complemant 4 protein was not affected ($p<0.05$ and $p>0.05$, respectively). Signs and symptoms of arthralgia. carditis, nephritis, myalgia, pleurisy and thrombocytopenia were improved. The treatment was well tolerated, except broncospasm in one patient. In conclusion, IVIG therapy has beneficial effects in active SLE patients with renal involvement.

Key Words: *Intravenous immunoglubulin treatment, Systemic Lupus Erythematosus*

Recently, IVIG has increasingly been used in the treatment of a large number of autoimmune and systemic inflammatory diseases (1-3). Some of these diseases are mediated by autoantibodies, others are believed to be dependent on autoreactive T cells; for some diseases, the autoimmune origine is only presumptive. The mode of action of IVIG in regulating autoantibody responses and in autoimmune diseases are still unclear. The immunomodulatory effects of IVIG are postulated to result from several possible complex interactions that ultimately have the capacity to down-regulate dysfunctional immune responses. These include: interference with Fc receptor function; down-regulation of antibody production through Fc receptor interactions; alterations in T cell subsets and T cell function; inhibition of inflammatory mediator release; inhibition of complement-mediated cytolysis; solubilization of immune complexes and regulation idiotype and anti-idiotype antibodies (4-8).

Current therapies for SLE include the use of corticosteroids and immunosuppressive drugs for those patients with more serious forms of the illness. Although there are numerous case reports claiming the efficacy of IVIG in the treatment of diverse manifestations, there are no randomized controlled trialsuntil yet. The therapeutic application of IVIG has been reported in a variety of SLE-associated immune cytopenias (9,10), the psychosis secondary to SLE (11), Kawasaki disease (12), Churg-Strauss syndrome (13), Guillain-Barre syndrome (14) and dermatomyositis (15).

The aim of this study is to investigate the effect of high dose IVIG on various organ manifestations (especially renal) and serological variables in systemic lupus erythematosus.

MATERIALS AND METHODS

Treatment and outpatient follow ups were performed in the Department of Immunology, Medical School of Ankara, İbn-i Sina Hospital. Eight patients with active renal involvement disease (all of them female, mean age was 25.8 ± 8.1, mean disease duration was 30.5 ± 16.1 months) were enrolled in the study. They full filled the American Rheumatism Association, criteria for the classification of SLE 1982 (16). All patients had clinically active SLE and they were

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refractory to conventional corticosteroid and/or immunosuppressive therapy. One patient had pneumonia addition to SLE. The manifestations were fever (8/8), arthritis (3/8), malar rash (7/8), cutaneous vasculitis (1/8), lymphadenopathy (2/8), hepatosplenomegaly (4/8), pleuritis (5/8), pericarditis (5/8), myalgia (6/8), lupus nephritis (8/8), Raynaud's phenomenon (4/8), psychosis (2/8), depression (2/8).

The following laboratory studies were performed for all patients: erythrocyte sedimentation rate (ESR), red blood cell, white blood cell and platelet counts, blood urea (BUN), serum creatinine, creatinine clearance, urinary proteins, C3 and C4 components, serum IgG, IgA and IgM levels and antinuclear antibodies (using by Hep 2 cell substrate, Promesan, Milano, Italy). Anti-ds DNA was analysed by Farr assay. All patients were tested for B and C hepatitis and HIV infections before and during IVIG therapy.

Renal biopsy were performed to all patients before the study and renal involvement was detected in all of them. In the majority of renal biopsy speciemens, diffuse proliferative glomerulonephritis (GN) (n=4) was demonstrated. Three patients had membranous GN and 1 had focal proliferative GN. The patients with lupus nephritis were considered to have active nephritis with the presence of abnormal urinary sediment, including hematuria and/or cellular casts, abnormal proteinuria (>0.5gr/day) and deteriorating renal function. None of the patients had hypertension and creatinine clearance were within normal limits.

Overall disease activity was measured in each patient before, during and after IVIG treatment, by SLAM score (17). Twenty-five symptoms and organ manifestations and 7 nonimmunologic laboratory variables were evaluated according to SLAM score.

All patients were given 400 mg /kg /day 4. generation IVIG preparation (Octagam. Octapharma, Pharmazeutika Wien, Austria) in each of 5 consecutive days of each month, for a six month period. Concomitant therapy was consisted of prednisolone for all patients (dosage range 10-30 mg/day). Clinical and laboratory data were assessed every month. Possible side effects were carefully assessed during and after each infusion.

Statistical analysis; Initial clinical and serological data of 8 patients were compared with corresponding values after therapy, and the significance was checked by using the Wilcoxon test for paired samples.

RESULTS

An improvement in clinical symptoms was observed in all patients after three cycles of therapy. The clinical findings, before and after IVIG therapy are shown in Table 1. The mean score of disease activity was significantly reduced during the course of therapy from 19.0 ± 5.9 (12-26) to 4.3 ± 2.4 (2-10) by the 6th month ($p<0.001$).

No significant changes in hemoglobin values were observed. The mean pretreatment and post treatment were as follows; hemoglobin values were 9.64 ± 2.14 g/l and 10.54 ± 1.76 g/l. The mean platelet and leukocyte counts were increased to 280875 ± 56273/mm^3 and 6075 ± 1351/mm^3 after IVIG therapy respectively ($p<0.05$ and $p<0.01$). No significant changes in BUN, serum creatinine levels and creatinine clearance were observed. Urinary proteins decreased from 2.22 ± 1.07 gr/L to 0.65 ± 0.85 gr/L ($p<0.01$). Serum C3 level was significantly increased from 0.25 ± 0.14 gr/L to 0.60 ± 0.28 gr/L ($p<0.05$). IVIG therapy had little effect on serum C4 level ($p>0.05$). A significant decrease in the anti-ds DNA titer was documented after IVIG therapy ($p<0.05$). The above results are shown in Table 2.

All patients were negative for B and C hepatitis and HIV infections. IVIG therapy was generally well tolerated in all patients. Three patients experienced facial flushing and headache. During the 6th infusion one patient suffered from broncospasm.

DISCUSSION

Systemic lupus erythematosus is a chronic autoimmune disorder with unknown aetiology characterized by the presence of B cell activation and autoantibodies production. SLE is a multisystemic disease.

Table 1: The Clinical findings of all patients, before and after IVIG therapy

	Before therapy	After therapy
Fever	8/8	-
Alopecia	8/8	6/8
Rash	7/8	3/8
Pericarditis	5/8	-
Pleurisy	5/8	-
Raynaud's phenomenon	4/8	4/8
Hepatosplenomegaly	4/8	1/8
Neurological involvement	4/8	4/8
Arthritis	3/8	-
Lympadenopathy	2/8	1/8
Cutaneous vasculitis	1/8	-

Table 2: The laboratory findings and SLAM score of all patients, before and after IVIG therapy

	Before therapy (mean value)	After therapy (mean value)	p
SLAM Score	19.0±5.9	4.3±2.4	p<0.001
Hemoglobin g/L	9.64±2.14	10.54±1.76	P>0.05
Platelet count/mm^3	137000±89493	280875±56273	p<0.05
Leukocyte count/mm^3	3673±1684	6075±1351	p<0.01
C3 level gr/L	0.25±0.14	0.60±0.28	p<0.05
C4 level gr/L	0.18±0.12	0.24±0.15	P>0.05
Anti-ds DNA level IU/ml	97.63±59.35	16.68±15.82	p<0.05
Proteinuria g/day	2.22±1.07	0.65±0.85	p<0.01

Drugs used currently for SLE such as corticosteroids and cytotoxic agents have serious side effects when used in higher doses recommended for life threatening disease.

The efficiency of IVIG in the treatment of patients with SLE has already been demonstrated (10,18-21). It is suggested that IVIG modulates macrophage-T cell function and increases suppressor T cell function (22, 23). The therapeutic application of IVIG has been reported in a variety of SLE-associated immune cytopenias (20,24,25) and life threatening situations (26). During IVIG therapy, it has been reported that transient neutropenia developed in patients with SLE (27,28). The therapeutic response has generally been transient, but prolonged remission has occasionally been reported (29). IVIG has also been reported to be corticosteroid-sparing in the treatment of serositis and cutaneous vasculitis in SLE and to be succesfull in SLE with cerebritis (11,18,20,26,30-32). Severe pulmonary and pleural manifestations have also been reported to positively respond to IVIG therapy (24,26). In our study we found that therapy continued with IVIG might control the disease, as the majority of our patients showed a regression of fever, skin rash, arthritis, as well as the regression of pericarditis and pleurisy, hepatosplenomegaly, cutaneous vasculitis, renal abnormalities, leucopenia, thrombocytopenia and anti-ds DNA antibody levels. However we did not observe positive response to Raynaud's phenomenon and neurological involvement. There are some studies showing the succesfull use of IVIG therapy psychosis secondary to SLE (11,20).

It has been reported that IVIG therapy is not beneficial in all SLE patients. Variations in the pharmacologic preparations of IVIG also may influence the outcome. Several groups have reported a worsening of proteinuria in patients with SLE who were treated with IVIG (20, 33) especially including sucrose or glucose as stabilizers (34). We used IVIG (Octagam, Octapharma) which consisted of maltose as stabilizers. In our study, we observed significantly reduced proteinuria and haematuria in all our SLE patients with renal involvement. Renal functions were stable during monthly IVIG infusions. It is reported in some cases that a frequent increase in disease activity could be seen in a few weeks or months after the last IVIG infusion (9,35). In our study, only one patient attented with increased disease activity after 15 days from the last infusion, but there was no deterioration in renal function.

Lin et al. (36) have demostrated that glomerular deposits containing immune complexes can be solublized in tissue sections obtained from SLE patients when incubated with human IgG. They observed a decreased proteinuria and circulating immune complexes with short courses of IVIG. This phenomenon could explain the improvement in renal function observed in our patients during the six months of therapy with IVIG.

IVIG therapy did not cause important side effects. In addition, it proved to be effective in suppressing disease activity. Furthermore, the dose of corticosteroid therapy was progressively reduced. This therapy is not only extremely expensive but also its longterm effects is not known. IVIG therapy can be used when corticosteroids or cytostatic are ineffective contrindicated or in patients with accompanying infections or those who are pregnant. IVIG had beneficial effects in active SLE patients with renal involvement. Further investigations are needed to show the efficiency of IVIG therapy in active SLE patients with renal involvement.

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MANAGEMENT OF HIRSCHSPRUNG DISEASE A CLINICAL REVIEW

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SUMMARY

A retrospective analysis was made of 45 patients admitted from January 1984 to 1996.

34 patients were male and 11 were female, yielding an overall sex ratio of 3:1. The age at diagnosis was younger than 30 days in 14 neonates (31%), 1 month to 1 year in 11 infants (24%), and older than 1 year in 20 children (45%).

Associated abnormalities were seen in 6 cases (13%) including Down syndrome in four, VSD+PS+situs inversus and VSD+ASD in one case.

Clinical presentation in HD included constipation, abdominal distantion, failure to thrive, billious vomitting, fecal soiling and encopresis. Delayed passage of meconium in 48 hours of life was the cardinal symptom in neonates.

Hirschsprung enterocolitis occurred in four cases.

Definitive operations were performed in 41 infants and children. Modified Duhamel procedure was used in 21 patients. Eight patients underwent anorectal myectomy, seven patients underwent Swenson operation and five patients underwent Soave-Boley operation.

Follow up evaluation was performed monthly for the first 3 months, every 3 months for 1 year and every 6 months thereafter until normal bowel function was achieved. Normal bowel function was defined as bowel movement 2 to 3 times a day without soling.

Key Words: *Hirschsprung disease, Diagnosis, Treatment*

Hirschsprung disease (HD) is still a diagnostic hallenge to the pediatrician and pediatric surgeon nce the classical description of congenital agangli- nic megacolon reported by Harald Hirschsprung in 886 (1). HD is a relatively common cause of intesti- l obstruction in neonates. Swenson and Bill reported new surgical treatment of HD in 1948. Modifications d new interventions have been described by Duha- el and Soave (2). Each procedure appears to be equ- y effective in correcting the disease, but the result is osely related to the skill of the surgeon as well as sur- cal procedures (3).

Diagnosis and surgical treatment of HD are now ll established, but there are still some problems in e diagnosis and management of this disease, particu- y in neonates (4).

HD is characterized by an absence of ganglion ls in the distal bowel beginning at the internal sfinc- and extending proximally for varying distances. e aganglionosis is confined to the rectosigmoid in 75% patients, the splenic flexure, or transverse colon in 17%, and the total colon along with a short segment of terminal ileum in 8% (3,4). Total intestinal aganglionosis with absence of ganglion cells from duedonum to the rectum is the rarest form of HD (5,6). The incidence of HD is estimated to be 1 in 5000 live births (4,6).

The aim of this study is to review the clinical features and management of HD, to obtain the reason of late admition and to correspond different diagnostic and surgical techniques.

MATERIALS AND METHODS

Medical records of 45 patients were reviewed for presenting symptoms and signs, demography. The existance of associated abnormalities, types of them were examined. The diagnostic procedures were classified, all roentgenograms and histopathological specimens were examined and corresponded with eachother. The type of operative techniques were reviewed

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and evaluated according to the results and complications.

RESULTS

A number of 45 cases were collected in this study, 34 patients were male and 11 were female, yielding an overall sex ratio of 3:1. The age at diagnosis was younger than 30 days in 14 neonates (31%), one month to one year in 11 infants (24%), and older than one year in 20 children (45%) (Fig. 1).

The diagnosis was made mostly with full - thickness rectal biopsies and colonography (Fig. 2, Table 1).

Aganglionosis was confined to the rectosigmoid in 37 (82%) patients, the splenic flexure, or transverse colon in 6 (13%), and the total colon with variable extension into small bowel in 2 (5%) cases.

Associated abnormalities were seen in 6 cases (13%) including Down syndrome in four, VSD+PS+situs inversus and VSD+ASD in one case.

Clinical presentation in HD included constipation, abdominal distantion, delayed passage of meconium, failure to thrive, vomitting, fecal soiling and encopresis (Table 2).

Hirschsprung enterocolitis occurred in four cases.

The use of colostomy or enterostomy before the procedure was selected by age at initial presentation. All except two patients had prelimenary colostomy or ileostomy. Definitive operations were performed in 41 infants and children. Modified Duhamel procedure was used in 21 patients. Eight patients underwent anorectal myectomy, seven patients underwent Swenson operation and five patients underwent Soave-Boley operation (Fig. 3). Three patients (10%) died before their definitive operation. One patient refused for his definitive operation

Twentyfive postoperative complications occured in 17 patients (Fig. 3). Nine intestinal obstructions, four anal incontinances, three postoperative enterocolitis, two anastomotic leakages, two postoperative herniation, two stenosis, one intra-abdominal haemorage, one rectourethral fistula and one invagination. There were six deaths in the entire group of 45 patients. Five occured in the neonatal and infant group. The causes of death were sepsis, and respiratory insufficiency.

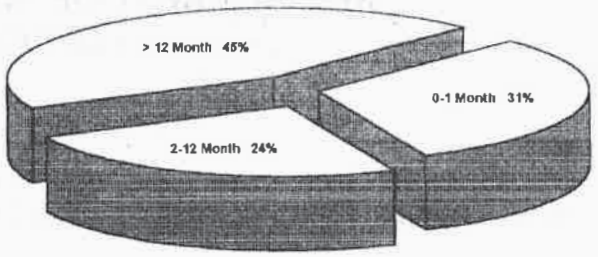


Fig. 1: The age at diagnosis was younger than 30 days in 14 neonates (31%), one month to one year in 11 infants (24%), and older than one year in 20 children (45%).

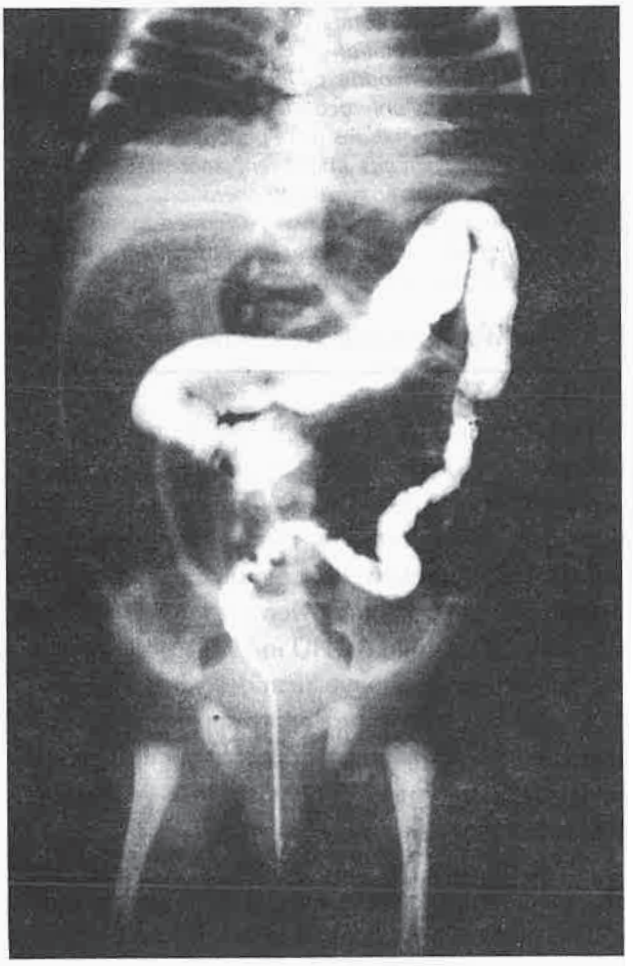


Fig. 2: Barium enema of a 4 month old male patient with Hirschsprung Disease. Proximal dilatation and distal contraction of the bowel.

DISCUSSION

HD is a neurogenic form of intestinal obstruction that still remains a cause of morbidity and mortality. The absence of parasympathetic ganglion cells in both the myenteric and submucosal plexuses of the bowel leads to an inappropiate interplay between parasympathetic and sympathetic autonomic innervation. This results in poor colonic propulsion in the involved bo

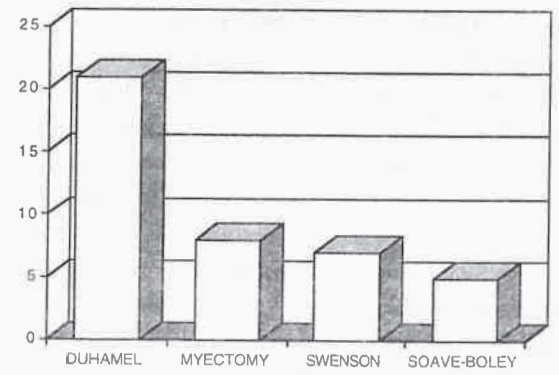
Table 1: Findings at full thickness rectal biopsies and colonographies in HD

Full Thickness Rectal Biopsy	Neonate 0-1 Month	Infant 2-12 Month	Children > 12 Month
Ganglion (-)	14	10	18
Deg. Ganglion	-	2	4
Neural Hypertrophy	3	4	4
Colonography Specific	6	3	5
Colonography Non-Specific	8	8	17

Table 2: Presenting signs and syptoms in HD

Signs and Symptoms	Neonate 0-28 Days	Infant 1-12 Month	Children > 12 Month
Delayed Passage of Meconium	13	4	4
Abdominal Distansion	12	8	6
Bilious Vomitting	10	3	4
Failure to Thrive	3	2	7
Constipation	3	6	13
Fecal Soiling	-	1	4
Encopresis	-	-	4

wel segment and the inability to relax the internal sphicter (2). In large series of patients with neuronal intestinal malformations which includes classical aganglionosis, hypoganglionosis, neuronal intestinal



ig. 3: Surgical proedures in HD.

dysplasia type A and B, immaturity of ganglion cells and not classifiable dysganglionosis, it was found that only one fourth suffers from HD (7).

Swenson and associates observed a male prodominance (80%), full - term infants (95%), a familial occurrence (7.8%), and a increased incidence of Down syndrome (3.2%) (8). The present study confirmed many previously reported demographic parameter; the male predominance and more frequent presence of rectosigmoid occurrence (3,4). Through colonic total aganglionosis was not detected, total colonic aganglionosis with extension into the small bowel was detected in two cases in this study.

Family history has been reported in 3% to 17% of HD cases, especially with total aganglionosis and in female patients (1,3). However, there was no family history in this study.

Down syndrome is the most frequently reported chromosomal abnormality and occurs in 3% to 9% of patients with HD (2,3,4). This incidence is well above the accepted frequency of 1 in 600 live births in the general population (8). In this study four (9%) out of 45 studied cases had Down syndrome.

Associated abnormalities are generally reported to be between 11% and 22% (3,4) In this study, 6 patients (13%) had 3 various abnormalities.

Enterocolitis remains the most serious complication of HD. The reported incidence of enterocolitis ranges from 7.2 to 19.8%(11). Enterocolitis occurred in four (9%) cases. One patient died on 3 month old age before his definitive operation due to inadequate ho-

Table 3: Postoperative complications in surgical procedures

Complications (25)	Duhamel	Swenson	Soave-Boley
Intestinal Obstruction (9)	6	2	1
Anal Incontinance (4)	1	2	1
P.O. Enterocolitis (3)	2	1	-
Anastomotic Leak (2)	1	1	-
P.O. Hernia (2)	1	1	-
Stenosis (2)	-	-	2
Recto-Urethral Fistula (1)	-	1	-
Internal Haemorage (1)	-	1	-
Invaginatin (1)	1	-	-

me nursing and late admission to the medical center with severe dehydratation, shock and sepsis. Three Hirschsprung enterocolitis occured postoperatively. The results were low when compared with literature. This has been related to Duhamel procedure, which postoperative Hirschsprung enterocolitis rate has been considered to occure low. On the other hand, almost 70% patient were diagnosed in infant and childhood period.

The syptoms in HD almost always date back to the neonatal period. Clinical presentations are neonatal obstruction, recurring obstructive episodes during infancy, chronic obstruction and diarrhea (14). HD is most (38%-64) diagnosed in the neonatal period (1.2). In the present series, 31% were diagnosed in the first month of life, 55% by the end of the first year. The analysis of the age at time of diagnosis is important because the delay of the diagnosis sometimes results in promotion of the incidence of enterocolitis. Diagnosis were made in 45% after 1 year of age. I

The diagnosis of HD has been well established by means of various methods such as barium enema, anorectal manometry, histochemistry by acetylcholinesterase activity on rectal suction biopsy, rectal full - thickness biopsy, and open biopsy. The error in interpreting barium enema was highest in the lower age group, especially in patients less than 1 month of age. The error was also high in patients with aganglionosis limited to the rectum and in patients with involvement to the hepatic flexure or higher (2,8). The overall error rate of barium enema was 11.7% (8). We performed in all patients colonography by clinical suspicion (Table 1). The overall error rate was as high as 31.1%. It was 43% in neonates, 27% in infants and 23% in children. The error decreased with the age of the patient. Specific finding of construction and dilatation of the proximal colon has mostly not occured yet in early diagnosis in neonates. However delayed film at 24 hours alter barium enema may then confirm the diagnosis by demonstrating retained barium (6). Colonography should be performed by experienced radiologists, since it is difficult to perform colonography in neonates. Rectal biopsy, as described by Swenson, Fisher, and MacMahon, has proved to be 98% accuracy (8). We had the similar results (Table 1). All patients underwent full thickness rectal biopsy by suspicion of clinical and/or colonography. Absence of ganglion cells in 95% and neural hypertrophy in 24% were detected.

One patient expired of Hirschsprung enterocolitis in delay of diagnosis. Colonography had false negative result and rectal biopsy was not diagnostic. In twelve neonates full thickness rectal biopsy or biopsy during other intestinal surgeries showed absence of ganglion cells. They survived without any clinical problems and no need of surgery. We should be aware of false negative results, so diagnosis must depend on more than one detections. Attempts to develop a blood test by estimation of serum and erythrocyte acetylcholinesterase activity may be a test for the future (17). It would avoid the need for a full thickness biopsy.

Whether an initial colostomy is needed or not is still controversial. The safe age for a definitive operation with good functional result is not yet standardizised. Ikeda et al (4) reported that enterostomy was created mostly under 1 month old, because the clinical signs were more severe and life threating in the neonatal period.

Most surgeons traditionally performed the Duhamel operations 6-15 months of life (6,12). Carcassonne et al (11) reported that the results of their series proved that currative surgical treatment of HD is satisfactory in patients younger than 3 months of age, and preoperative decompression by a routine colostomy was not necessary. In recent years, most cases of HD are diagnosed during the neonatal period. Many centers are now performing one stage pull - through operations in newborns with minimal morbidity and encouraging results (3). In the present series, HD were mostly diagnosed until 6 months of age. Decompression o the colon was inevitable. We performed preliminary colostomy in neonates until they reached 6-9 month of age and also in infants and children for 3-4 month before the definitive operation. Surgical correctio without preliminary colostomy was performed in tw infants. The results were good. So we also agree tha preoperative decompression by a routine colostomy i not necessary in patients younger than 3 months age

Various operative procedures have been succes fully performed in the treatment of patients with HD Each procedure appears to be equally effective in co recting the dissease, but the result is closely related t the skill of the surgeon (3). In the present study mod fied Duhamel procedure was used in 21 patients. Eigl patients underwent anal myectomy, seven patients u derwent Swenson operation and five patients unde went a Soave-Boley operation. The Duhamel operat on for HD avoids the extensive pelvic dissection ar avoids damage to the sensory fibers of the rectum th may be encountered during performance of Swens

operation. The Duhamel procedure also avoids the mucosal dissection of the rectum by the Soave endorectal pull-through procedure. The major disadvantage of the classic Duhamel technique was related to the occurrence of a fecaloma in the retained rectal pouch. Martin's modification of the procedure, which completely divides the entire colorectal spur, appears to have solved this problem (2). Duhamel (5) himself reported that retrorectal transanal pull-through has two particular aspects of the operation: Allows re-operation on failed cases and to perform in neonates.

Twentyfive postoperative complications occured in 17 patients of this series. Nine (20%) intestinal adhesive obstructions, four anal incontinances (9%), three (7%) postoperative enterocolitis, two (6%) anastomotic leakage and two (4%) stenosis were detected. Complication rates were similar like in literature. Intestinal obstructions were high in our series. Most patients were diagnosed late in childhood. Famillies evaluated HD as simple chronic constipation admitted late to a health center. Patients should have had multiple Hirschsprung enterocolitis. Proximal colon dilatation and edema improves and performs a chronic form in patients who survives. In some their first clinical presentation was ileus when they admitted the emergency service. We considered intestinal obstruction to be high to these reasons. On the other hand, four patients had more than once (2-3) time presentation of intestinal obstruction. The complications were relatively high in the Duhamel group. This was related that 50% of the surgical procedures were Duhamel and 18% were myectomy. Anal incontinance and recto-urethral fistula were seen in Swenson procedure which were related to extensive pelvic dissection. Stenosis were only seen in Soave-Boley procedures as expected. To prevent stenosis during pull-through, forcefull dilatations and internal sfincterectomy have been done for preparation.

It has become customary to recognize clinical groups and more and more are recognized especially in the neonatal period as pediatricians and pediatric surgeons become aware of the early syptomatology, so that the dangers of delay in diagnosis and treatment can be eliminated. The age at time of diagnosis decreased when compared previous reports in this country.

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ACUTE AORTIC REGURGITATION DUE TO LIBMAN SACKS ENDOCARDIT COMPLICATED BY INFECTIVE ENDOCARDITIS: A CASE REPORT

Mehmet Kabukçu* • Serdar Aksöyek* • Lale Tokgözoğlu* • Metin Demircin*

SUMMARY

Hemodynamically significant valve lesions in systemic lupus erythematosus are rare. A patient with systemic lupus erythematosus who developed refractory heart failure and severe acute aortic regurgitation due to Libman-Sacks disease complicated by infective endocardits which necessitated valve replacement is reported here. In considering to the etiology of severe pulmonary edema caused by acute valvular insufficiency, the Libman Sacks endocarditis complicated by infective endocarditis should be considered in patients with SLE.

Key Words: *Acute aortic insufficiency, Libman-Sacks endocarditis, Systemic Lupus Erythematosus*

Involvement of the cardiac valve is generally not a prominent feature in systemic lupus erythematosus. When present, the classical heart valve lesion in SLE is low grade endocarditis with Libman Sacks verrucous vegetation on the mitral valve (1). Verrucous endocardial lesions are ovoid, usually less than 4 mm in diameter and generally have no hemodynamic significance. Rarely the valvular lesion in SLE may be complicated with thromboembolism, endocarditis and need for cardiac surgery (2). The verrucous endocardial involvement in SLE poses an increased risk of infective endocarditis, particularly in the immunosuppressed patient (1,2). Aortic valve involvement in SLE is less than mitral valve involvement (3,4). We report a young patient with systemic lupus erythematosus and enterococcal infective endocarditis who presented with acute pulmonary edema resulting from severe acute aortic insufficiency.

CASE REPORT

A 30 year old female who had been diagnosed with SLE at 26 years of age and was treated with prednisolone 60 mg/day and intermittent endoxan (500 mg/ month) was admitted to the hospital because of fever of unknown origin. Two months before presentation in a laboratory examination, Antinuclear antibodies was positive at 1/160 titer, anti-native DNA antibodies 619 iu/mL (0-100 iu/mL), complement component 3 59 mg/dL (85-100 mg/dL), and complement component 4 10mg/dL (12-40 mg/dL) were found. Four days before admission, she experienced high fever, headache and malaise. The patient had not had any gastrointestinal or genitourinary instrumentation or dental extraction. On admission, she presented with mild confusion, high fever (39 °C), hypotension (70/40 mm Hg), petechial skin lesions and thrombocytopenia (15000/mm^3). At laboratory examination the hemoglobin was 7,8 gr/dl, leukocyte count 5700/mm^3, erythrocyte sedimentation rate was 63 mm/hour, and the C-reactive protein was 43 mg/dl. Community acquired sepsis in the immunosuppressed patient and SLE activation diagnosis were made. Imipenem 500 mg four times was given intravenously. The patient's fever was controlled but her dyspnea increased and hypoxemia developed. Her urea and creatinine values were increased progressively and at the fourth day severe acute dyspnea occurred, fine crepitation was heard bilateral lung fields and a mild early diastolic murmur appeared. Amikacine and vancomycine were added. An echocardiographic examination demonstrated normal left ventricular contraction pattern, and a large vegatation at the tip of the right coronary cusp of the aortic

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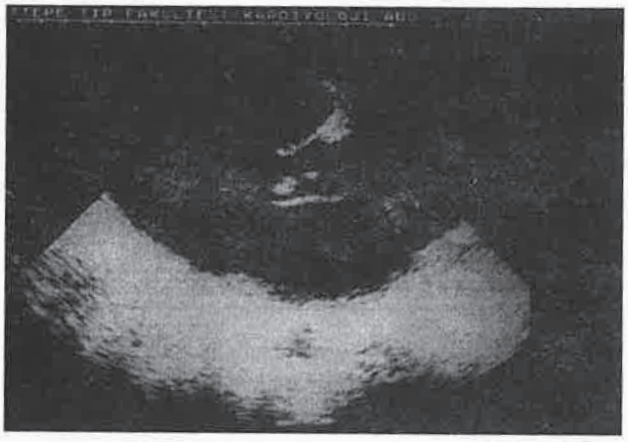

Fig. 1: Echocardiographic examination from parasternal long axis examination reveals a large vegatation at the aortic valves

valve (Fig 1). Doppler examination showed severe aortic regurgitation (3/4) and mild mitral regurgitation(2/4). Dobutamine and nitroglycerin infusion were performed. Due to hyperpotassemia and hypervolemia hemodialysis was performed. Enterococci were grown in all three blood cultures. Antibiotic therapy was changed to Penicillin G 20.000.000 iü/day and gentamicin 40 mg bid. At the tenth day, the patients hemodynamic status was stabilized and she underwent open heart surgery. At operation vegetation were seen on the right and noncoronary cusps and also an irregular tear under the vegetation was found at the right aortic cusp. Lung biopsy was taken. Aortic valve replacement was performed. Aortic valve culture showed no bacteria. Lung biopsy was nonspecific. The patient's postoperative period was uneventful. With conservative treatment congestive heart failure was controlled. Renal function tests returned to normal levels. Two months after surgery our patient was well and control echocardiograms showed normal functioning of the prosthetic valve.

DISCUSSION

The heart is frequently involved in patient with SLE (1,2). Several clinical and postmortem studies demonstrated a high incidence of cardiovascular involvement such as pericarditis, myocarditis, verrucous endocarditis, heart block and coronary arteritis (2,5). In echocardiographic studies the incidence of aortic regurgitation is similar to control groups (6). The classical heart valve lesion in SLE is low grade endocarditis with vegetation formation on the mitral valve originally described by Libman Sacks (1,2). Valvular heart disease in SLE sometimes might be complicated by congestive heart failure requiring valve replacement, thromboembolism and bacterial endocarditis (2,7).

In Libman Sacks endocarditis most of the vegetations seem to be in the area of mitral valve (5,8). Aortic valve involvement is relatively rare and has been found only in 4.6 % of autopsy studies (2,5). The Libman Sacks endocarditis is thought to be about 5 % which is much higher than the prevalence in the normal population and other collagen vascular disease (2,5,9). Both the immunsupressed state of the patient and the sterile vegetation are thought to predispose to infective endocarditis. The immunosupressive state in SLE is thought to be due to chemotaxis, phagocytosis, and killing defects in the immune system due to corticosteroid and immunosupression therapy (9,10).

Whether the valve lesion is due to infective endocarditis or Libman Sacks disease is extremely difficult to differentiate. The echocardiography location, appearance and mobility of valve masses might be useful parameters in the differential diagnosis (8). Lupus associated valve lesions are predominantly located near the leaflet base, have a heterogeneous density and move exactly parallel to the motion of the related valves. On the other hand infection associated valve lesions are generally located at the tip of the leaflet, have a homogenous density and move at least partially vibratory and rotatory motion (8). In our patient, a dense large vegetation approximately 1cm was located at the tip of the right and noncoronary cusp of the aortic valve. Despite appropriate steroid and immunsupressive treatment a vegetation larger than 0,5 cm and location of vegetation was also consistent with infective endocarditis rather than Libman Sacks disease.

Although half of the patients with SLE have Libman Sacks endocarditis, severe valvular regurgitation is rare. A few patients have required mitral valve replacement and even fewer aortic valve replacement due to heart failure (3,4,7). Steroid use is thought to exacerbate the valvular disease although they improve the systemic manifestation of SLE leading to fibrosis and shrinking of the valvular tissue (5,8).

Our patient's clinical presentation is unusual. She had active lupus despite steroid and immunosupressive treatment and infective endocarditis superimposed on the Libman Sacks endocarditis lead to a tear of the

right coronary cusp causing acute aortic regurgitation leading to pulmonary edema. In considering to the etiology of severe pulmonary edema in patients with SLE, acute valvular insufficiency due to Libman Sacks endocarditis complicated by infective endocarditis should be remembered.

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SUPERIOR VENA CAVA SYNDROME: CAUSED BY LUNG CANCER ASSOCIATED WITH CHRONIC LYMPHOCYTIC LEUKEMIA

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SUMMARY

We present here a patient with vena cava superior syndrome caused by lung cancer and at the same time was found to have chronic lymphocytic leukemia(CLL).

Key Words: *Chronic lymphocytic leukemia, Lung cancer, Vena cava superior syndrome*

Superior Vena Cava (SVC) obstruction is caused by cancer in 85-90% of affected patients. The etiology of SVC in patients with a malignancy is 80-90% lung cancer, 10-20% lymphomas, and other such miscellaneous tumors as embryonal sarcoma, metastatic breast, bladder or gastric carcinomas, germ cell tumors, melanoma, mesothelioma and thymoma. Other etiologies are thrombosis, aneurysm, goiter, mediastinal fibrosis, indwelling catheters and trauma(1-3). The manifestations depend on the rapidity of tumor growth, presence of intraluminal clot, and the degree and level of obstruction. Early histologic diagnosis of the tumor that causes a SVC obstruction is crucial since the treatment of choice for chemosensitive tumours is immediate chemotherapy. Other tumors should be treated with radiotherapy (1-3). We present our observations of a patient with newly diagnosed CLL who developed SVC obstruction from a synchronous lung cancer.

CASE REPORT

A 58 year old heavy smoker man was admitted to the hospital because of general malaise, weight loss, cough, sputum, dispne and haemopthysis. There was eight months of history of fatigue and two weeks of history of the other complaints. On physical examination there was facial congestion and bilateral jugular vein distention. The WBC was 42.650 with 95% small lymphocytes with condensed nuclei, hemoglobin 10.5g/dl, platelets 188 x 109/l, erythrocyte sedimentation rate was 135mm/h. Chest X-ray revealed that right hemidiaphragm was elevated, and right costophrenic sinus was blunt. There was a nonhomogeneous shadow in the right midlung zone which was superposed over right hilum. Computed tomography scan of the chest showed a mass of the right hilar region which compressed on the right main bronchus. Fiberoptic bronchoscopy revealed right upper lobe bronchus obstruction and infiltration in the right main bronchus. The diagnosis of epidermoid carcinoma of the lung was established by bronchial biopsy.

Abdominal USG, cranial CT scan and bone sintigraphy was normal. Stage 0 CLL diagnosis was made by peripheral smear and bone marrow studies. Palliative radiation therapy with 38 Gy was planned to the mediastinum and right hilum. Pneumonia and right pleural effusion developed during radiotherapy. Pleural fluid examination was consistent with emphyema. Antibiotherapy and chest tube drainage were applied. The patient died of pneumonia and empyhema on the tenth days of therapy.

DISCUSSION

The most frequent cause of SVC is bronchogenic carcinoma. Enlarged hilar lymph nodes or a widened

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mediastinum were detected radiographically in 5% of CLL patients (4). CLL almost never causes SVC and over a quarter of patients with CLL are asymptomatic at diagnosis. In patients with lymphocytic leukemias, pulmonary infiltrates and malignant pleural effusions are more commonly associated with the chronic rather than the acute form of the disease. Such patients will almost always have evidence of other sites of tissue involvement, especially in lymph nodes, liver, and spleen, in addition to pulmonary or pleural invasion (5-7). There was no infiltration of CLL in the lung in our patient. Right hilar mass was due to the lung cancer. The diagnosis of CLL was made during routine blood analysis. The risk of secondary malignancies are higher in CLL patients than in general population. The most frequent second tumors are melanoma, soft tissue sarcoma, and colorectal and lung carcinoma (1,8,9). Despite increased frequency of secondary malignancy in CLL, simultaneous malignancy is not frequent. Therefore we present here a patient who had CLL, lung cancer and SVC at the same time. İn the literature it has been shown that there was one similar case reported (1). İn this case CLL was the cause of the SVC obstruction.

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AUTOIMMUNE CHRONIC HEPATITIS IN CHILDHOOD TRIGGERED BY ACUTE HEPATITIS A

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SUMMARY

Hepatitis A virus is responsible for the vast majority of acute hepatitis in childhood. Although it is well established that prognosis is good and there is no risk of chronic hepatitis, recent evidence suggests that hepatitis A may play a role in triggering autoimmune hepatitis. We present two girls, 8 and 14 years old who developed autoimmune chronic active hepatitis after acute hepatitis A.

Key Words: *Hepatitis A, Autoimmune hepatitis, Childhood*

Acute hepatitis A in children is an acute hepatic inflammation without chronic sequelae. However it has recently been reported that in certain individuals, with a genetic predisposition to the development of autoimmune hepatitis, HAV infection may be the precipitating event in the pathogenesis of this disorder (3,5). We report two cases of acute hepatitis A in whom autoimmune chronic active hepatitis developed.

CASE REPORT

Case 1

An 8 year-old-girl was evaluated in our hospital because of an acute onset of malaise, fatigue, anorexia, vomiting and dark urine. Physical examination revealed jaundice and a mild hepatomegaly. Acute hepatitis A was diagnosed based on laboratory evidence of acute hepatocellular injury (AST: 295 U/L, ALT: 855 U/L, T. bilirubin: 9.20 mg/dl, Direct bilirubin: 3.40 mg/dl) and the presence of Ig M Anti HAV. The patient remained symptomatic with hyperbilirubinemia and elevated aminotransferase levels through four months of follow-up. She was admitted to hospital because of prolonged course. Physical findings were jaundice, a hepatomegaly of 7 cm and a splenomegaly of 2 cm below the costal margin. Her laboratory values were as follows: AST: 464 U/L, ALT: 481 U/L, AP: 366 U/L, GGT: 55 U/L, T. protein: 10 gr/dl, albumin: 4.2 gr/dl, T. bilirubin: 11.03 mg/dl, D. bilirubin: 3.57 mg/dl, ESR: 110 mm/hr, PT: 12 and PTT: 28 sec.

Tests for HB_sag, Anti HB_C IgG and Anti HCV were negative, Ig G EBV was positive. Ceruloplasmin 60 mg/dl, Serum Cu: 116 microgram/dl and urine Cu was 60 microgram/24 hr. The Ig G level was 41.07 g/L, antinuclear antibodies were negative whereas Anti DNA: 6.9 mU/L (range: 0-7 mU/L) and anti-smooth muscle antibodies were present in a titer of 1:20. An abdominal ultrasonography was performed which revealed hepatosplenomegaly and lymphadenopathies in the portal hilus.

She developed a rash on her legs which was diagnosed as leucocytoclastic vasculitis with biopsy. A liver biopsy was performed, which was consistent with active cirrhotic process with a Knodell score of 21. Cooper staining was negative and hepatic copper concentration was 40 mg per gram of dry weight of liver. She was put on steroid therapy, with a diagnosis of autoimmune hepatitis. Serum T_3, T_4 and TSH were within normal limits and thyroid antimicrosomal antibodies as well as antithyroglobulin were negative.

Serum aminotransferase levels fell within the first week of therapy, to near normal values (AST: 45 U/L,

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ALT: 54 U/L) whereas serum bilirubin levels (T. bilirubin: 5.53 mg/dl and direct bilirubin 1.4 mg/dl) as well as Ig G (36.69 gr/L) were still above normal limits.

Approximately two months after the initiation of steroid treatment, physical examination, serum aminotransferases, serum bilirubin and Ig G were normal and no symptoms attributable to liver disease were reported.

At present, she is Ig G Anti HAV positive and Ig M anti HAV is nondetectable.

Repeat liver biopsy showed improvement with lymphocytic infiltration in hepatocytes and perisinusoidal cholestasis. The patient is currently on maintenance steroid therapy and asymptomatic with normal aminotransferase and immunoglobulin levels.

Case 2

A 14 year-old-girl was admitted to our hospital because of jaundice, malaise, fatigue, anorexia and dark urine of two months duration. She appeared in good health except for jaundice and a mild hepatomegaly. Serum aminotransferase levels (ALT: 1666 U/L, AST: 2572 U/L) and serum bilirubin levels (T. bilirubin: 45.90 mg/dl, direct bilirubin: 8.06 mg/dl) were very high. Acute hepatitis A was diagnosed based on the presence of Ig M Anti HAV. HB_sag, Anti HB_C Ig G and Anti HCV were negative, Ig G CMV was positive. Three months after her symptoms had began, her aminotransferase and bilirubin levels were still high (ALT: 430 U/L, AST: 633 U/L, T. bilirubin: 7.83 mg/dl, D. bilirubin: 1.55 mg/dl); therefore a diagnostic work-up was planned.

Kayser-Fleischer ring was not seen and serum ceruloplasmin level was normal (34 mg/dl). Her Ig G level was 30 gr/L, antinuclear antibodies, Anti DNA and antimitochondrial antibodies were negative whereas anti-smooth muscle antibody was positive in a titer of 1:20. Serum thyroid hormone levels and TSH were within normal limits, thyroid microsomal antibodies and antithyroglobulin were negative.

Abdominal ultrasonography revealed a mild hyperechoic and heterogenous hepatomegaly and minimal splenomegaly. Doppler ultrasonography was normal A liver biopsy was performed which was consistent with chronic active hepatitis with a Knodell score of 15. Steroid therapy was instituted. Serum aminotransferase levels, bilirubin levels as well as Ig G level was within normal limits in two months.

At present she is free of symptoms, with normal physical examination and normal laboratory values, and is on maintenance steroid therapy.

DISCUSSION

Autoimmune chronic active hepatitis is characterized by periportal piecemeal necrosis accompanied usually by high serum titers of non-organ specific autoantibodies and by hypergammaglobulinemia (1). Although the pathogenesis of autoimmune hepatitis remains unclear, a genetic predisposition to the disease is undoubtedly present (5). The mechanisms responsible for ongoing liver injury are not fully understood. It is believed to be mediated by a cellular immune response to self encoded antigens expressed on the hepatocyte membrane (4), and there is a defect of specific supressor-inducer T lymphocytes in these patients (6). Autoimmune chronic active hepatitis is thought to be triggered possibly by viruses or drugs which induce a helper T cell response against liver cell surface antigen (2), and it has recently been suggested that hepatitis A virus may play a role in initiating autoimmune hepatitis (3,5). Hepatitis A virus is responsible for the majority of acute hepatitis in children with a favorable course. Although occasionally the course may be relapsing or cholestatic, it is widely accepted that there is no risk of chronic hepatitis. The patients presented here had an acute onset of hepatitis with prodromal features and had the serological evidence of hepatitis A. As their course prolonged, they were re-evaluated. Autoimmune hepatitis is diagnosed based on the clinic, laboratory and histologic findings. The children showed a dramatic response to steroid therapy which is also one of the characteristic features of autoimmune hepatitis. Both of the cases developed antibody of Ig G type to HAV which ruled out the persistence of HAV infection.

The previously reported cases (3,5) and ours suggest that in some patients acute hepatitis A may not act as innocent as it is classically accepted and autoimmune hepatitis should be kept in mind in the differential diagnoses when a prolonged course of hepatitis A is discovered.

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CARDIAC RHABDOMYOMAS WITH PREEXCITATION IN A PATIENT WITH TUBEROUS SCLEROSIS (A CASE REPORT)

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SUMMARY

The rhabdomyoma, the most common cardiac tumour in infancy and childhood, is usually associated with tuberous sclerosis. Cardiac rhabdomyomas, although occasionally life-threatening, are increasingly diagnosed in patients with few or no symptoms. A case of short P-R interval without reciprocating tachycardia in a 9-months-old infant with tuberous sclerosis is described.

Key Words: *Preexcitation, Rhabdomyoma, Tuberous sclerosis*

Cardiac rhabdomyomas, although rare, are the most common primary cardiac tumours in infancy and childhood. They comprise approximately fifty percent of primary cardiac tumours in pediatric patients. Cardiac rhabdomyomas are closely associated with the syndrome of tuberous sclerosis (TS) (1,2). In this report we present an infant with TS who had cardiac rhabdomyomas with preexcitation.

CASE REPORT

Nine months old male infant, was born at term to healthy parents after an uneventful pregnancy and delivery. He appeared to be normal until 7 months. He admitted to Pediatric Neurology Department of Ankara University when he developed flexor spasms and he was diagnosed as TS with infantile spasms. He had multiple hypopigmented macules located on his trunk, buttocks, and on his chin. He had typical hypsarrhythmia on EEG. The CT scan showed calcified nodules in the periventricular area. There was no familial history of signs and symptoms of TS. He was referred to Pediatric Cardiology Department in part of routine diagnostic evaluation. He had no cardiac symptoms and his cardiac examination was completely normal. The ECG demonstrated an axis of + 50 and a short P-R interval (40 ms) (Fig 1). No arrhythmia was documented during his follow-up lasting 6 months. Chest x-ray film was normal. Echocardiographic examination of the patient showed well circumscribed, echo-bright two masses located in the left ventricular cavity. The large one (25x15 mm) was arisen from the left ventricular free-wall (Fig 2), and the small one (8x8 mm) was attached to the ventricular septum in the left ventricular outflow tract (Fig 3). There was no evidence of obstruction to blood flow due to these masses. The diagnosis of cardiac rhabdomyomas was established because of the clinical diagnosis of TS. ACTH and valproate therapy was started for infantile spasms.

DISCUSSION

Rhabdomyomas comprise approximately 50 % of primary cardiac tumours in pediatric patients and are considered the most common primary cardiac tumours in this age group (1-3). Close association of rhabdomyomas with TS are well known. In an autopsy series, 30 % of patients with TS were reported to have

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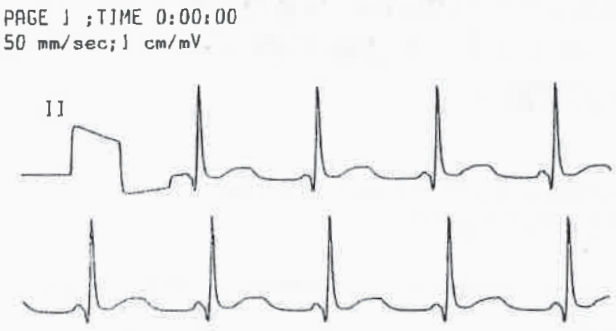

Fig. 1: Rhythm strip ECG recorded at 50 mm/s of the patient shows short P-R interval (40 ms)

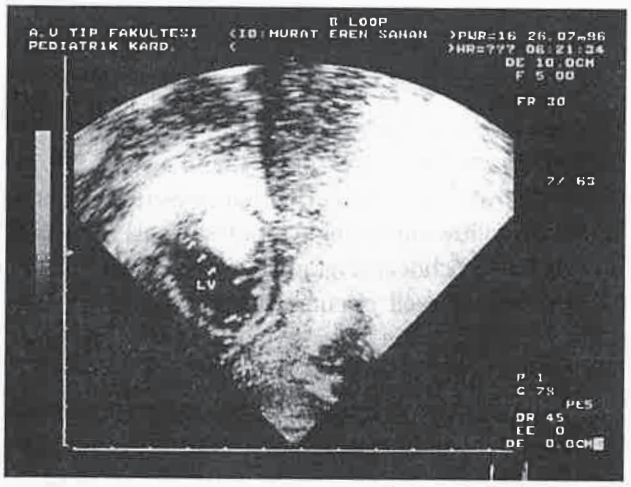

Fig. 2: Subcostal short-axis echocardiogram from patient showing a 25x15 mm mass (arrows) within the cavity of the left ventricle (LV)

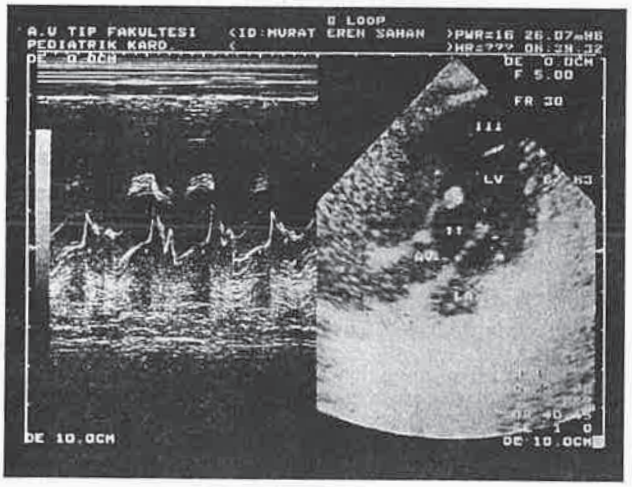

Fig. 3: Apical long axis echocardiogram from patient. An 8x8 mm mass (double arrows) is attached to the ventricular septum in the left ventricular outflow tract. AV = aortic valve, LA = left atrium, LV = left ventricle.

cardiac rhabdomyomas (1). However, recent echocardiographic study of Bass et al revealed a 50 % incidence of cardiac rhabdomyoma in patients with TS (4). Rhabdomyomas are usually multiple,often intracavitary well circumscribed tumours that can occur anywhere within the heart (1,3-5).

Cardiac signs and symptoms in a patient with rhabdomyoma may result from obstruction of blood flow from an intracavitary tumour, or diminished contractility from replacement of the myocardium or disturbances of cardiac rhythm (5-7). Earlier clinicopathologic studies indicated that the prognosis for cardiac rhabdomyoma was disappointing with fatality rates of 80 to 92 % by the age of 5 years (1). However with the widespread use of echocardiography, cardiac rhabdomyomas although occasionally life-threatening, are increasingly diagnosed in patients with few or no symptoms (5,8,9). Interestingly, recent echocardiographic follow-up studies clearly indicate that the spontaneous complete or near-complete regression of most cardiac rhabdomyomas is the rule, and that in the absence of life threatening complications (e.g. severe inflow or outflow obstructions, serious rhthym disturbances) conservative management is advised (5,8-10).

Our patient was diagnosed as having cardiac rhabdomyomas because of the clinical diagnosis of TS. These tumours can be diagnosed with reasonable certainty in infants with TS, even without histological proof. We decided to follow the patient for tumour regression without any intervention because of the lack of symptoms. He remained asymptomatic during the follow-up period of six months, and no tumour regression was documented by echocardiography.

Abnormal ECG findings include left axis deviation, atrial enlargement, ventricular hypertrophy and ST-T wave changes. Involvement of the conduction system can be demonstrated in the ECG that manifest bundle-branch block, preexcitation, or first- through third degree atrioventricular block (5-7,11). There was a short P-R interval in the ECG of our patient, a feature also reported in two patients with cardiac rhabdomyoma in the literature (3,7). One of the reported patients had bouts of reciprocating tachycardia. The author suggested that preexcitation syndrome and reciprocating tachycardia probably produced by impulse re-entry via accessory atrioventricular pathways in the tumour (3). We could not demonstrate any tumour located near or at the atrioventricular junction by echo-

cardiography to support this hypothesis. Although, it was possible that we could miss the small nodules especially if located intramurally.

Two-dimensional echocardiography is an invaluable tool of diagnosing cardiac rhabdomyomas in patients with TS. Regardless of symptoms, all patients with TS should be evaluated by echocardiography. Once, rhabdomyomas are identified, long-term follow-up of these patients for rhythm disturbances and tumour regression is also mandatory.

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A CASE WITH A VARIATION OF THE MEDIAN NERVE

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SUMMARY

Many variations are observed in the brachial plexus while giving off its branches. These variations are important because of leading to misdiagnosis and mistreatment. In this study we found a variation of the median nerve in a routine dissection of the left upper limb of a white male cadaver, age of 60 years-old and weight of 70 kilograms. Both the lateral and the medial roots of the median nerve joined near the insertion of the coracobrachialis muscle forming the median nerve. The musculocutaneous nerve only gave off muscular branches to the coracobrachialis and brachialis muscles. The muscular branch of the biceps brachii muscle originated directly from the lateral cord at the origin level of the coracobrachialis muscle.

Key Words: *Axillar surgery, Median Nerve, Musculocutaneous nerve, Variation*

The median nerve is formed by joining one branch from the lateral cord and one from the medial cord in front of the axillary artery. This nerve supplies the thenar muscles and the muscles of the forearm, except the flexor carpi ulnaris muscle and the ulnar part of the flexor digitorum profundus muscle. The musculocutaneous nerve arises from the lateral cord of the brachial plexus and supplies the biceps brachii, brachialis, and coracobrachialis muscles (1-6).

MATERIALS AND METHODS

A variation of the median nerve was found in a routine dissection of the left upper limb of a white male cadaver, age of 60 years and weight of 70 kilograms.

RESULTS

Both the lateral and the medial roots of the median nerve usually join anterior to the axillary artery, to form the median nerve. Both, however, joined near the insertion of the coracobrachialis muscle forming the median nerve in our dissection. The musculocutaneous nerve only gave off muscular branches to the coracobrachialis and brachialis muscles. The muscular branch of the biceps brachii muscle originated directly from the lateral cord at the origin level of the coracobrachialis muscle. Meanwhile, a branch in 1 mm diameter arose from the lateral cord, passed crosswise the axillary artery anteriorly and joined to the origin of the median root of the median nerve (Fig. 1).

DISCUSSION

Many variations of the median nerve were determined. According to Odar (6), the musculocutaneous nerve may not exist, in cases where the median nerve substitutes the nerve. As Gardner stated (2), the median nerve is formed in the middle of the arm in front of the brachial artery rather than in front of the axillary artery. Spinner and co-workers (7) observed that the median nerve and the musculocutaneous nerve run together and originated as a single branch from the lateral cord in two cases. Likewise, Haymaker and Woodhal (8) found in an operation that the median and the musculocutaneous nerve arose from the lateral cord as a single branch. İlgi and colleagues (9) described two similar variations in two cases. In both cases the musculocutaneous nerve perforated the coracobrachialis muscle and following; supplied the biceps brachii

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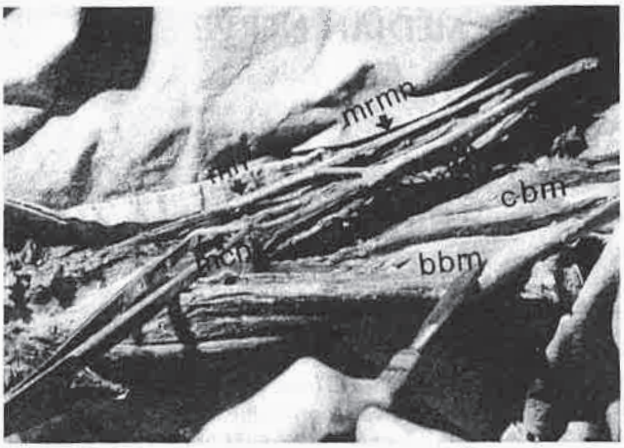

Fig. 1: Variation of the median nerve.
mn: The median nerve
mrmn: Medial root of the median nerve
lrmn: Lateral root of the median nerve
mcn: The musculucutaneous nerve
cbm: The coracobrachial muscle
bbm: The biceps brachii muscle

muscle and then joined with the median nerve through a branch in the first case; while joined with the median nerve through a branch and supplied the biceps brachii and the brachial muscles in the second one.

In our case the lateral and the median root of the median nerve joined near the insertion of the coracobrachialis muscle, differing from the other variations. The biceps brachii muscle was supplied by a muscular branch arising directly from the lateral cord at the level of the coracobrachialis muscle. In addition, a branch from the lateral cord passing crosswise the axillary artery anteriorly ended at the origin of the medial root of the median nerve.

As the conclusion, all those variations are clinically important, since they, for example, influence the trace of pains and cause misdiagnosis. Therefore, these and other similar variations should be considered in the diagnosis as well as the surgery of this region.

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