VOLUME 5 ISSUE 2

DECEMBER 2011

University of Duhok
College of Medicine

Duhok Medical Journal

The Official Journal of Duhok College of Medicine

ISSN: 2071-7326

Photo on the cover page

Gulshler flower

It is also called Crown imperial or Kaiser's Crown (Fritillaria imperialis) and is a member of the genus Fritillaria, family Liliaceae. This flower is native of the Nochiya region in the Middle East which is located in the heart of Kurdistan. Nochiya region is made up of 5 districts: Shamzidin, north eastern half of Shaqlawa District, Soran District, Mergasur District, and the western part of Urmia District. The flower grows to about one meter in height and flowering starts in late April or May.

Sources: http://en.wikipedia.org/wiki/Fritillaria_imperialis

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Duhok Med J

CONTENTS

EVALUATION OF ZINC STATUS AMONG PATIENTS WITH DIABETES MELLITUS

DHIA J. AL-TIMIMI, BSc (Pharm), MPhil, PhD*
HIVI M. MAHMOUD, MBChB, MSc**

Submitted 4 May 2011; accepted 11 Dec 2011

ABSTRACT

Background and objectives A general observation in diabetes, type 1 as well as type 2 is hypozincemia which may be the result of increased urinary excretion or decreased gastrointestinal absorption of zinc or both. The resulting decrease in total body zinc may contribute to diabetic complications. Hence, the present study was conducted to evaluate zinc status for diabetic patients, in an effort to identify diabetic group for whom zinc supplementation may be concern. The objective was to assess zinc status among randomly selected diabetic patients of Duhok city.

Methods Collection of data was carried out during the period from September 2009 to June 2010 at the Duhok Diabetes Center in Duhok Governorate/Kurdistan region/ Iraq. In the first part of the study (cross sectional study), a total of 362 subjects were involved. Among these, 206 were diabetic patients (type 1 DM, n=48; Type 2 DM, n=158) and the remainders were 156 apparently healthy subjects. In the second part of the study (intervention study), twenty eight type 2 diabetic patients were selected according to selection criteria and were supplemented with 40 mg elemental zinc as zinc gluconate per day for 3 months, from those 23 completed the trial. General information for each subject was obtained by questionnaire designed for the study. Fasting serum glucose (FSG), lipid profile, glycoselated hemoglobin (HbA1c) and serum zinc were measured for each subject.

Results The prevalence of hypozincemia was 33.0% for the 362 individuals included in the study. The prevalence was significantly higher in diabetic patients than healthy controls (43.7% vs 19.9%, P<0.01). To evaluate changes of zinc levels, relating for some epidemiological variables. However, no statistically significant effect was found using a P value of 0.05; for sex, BMI, central obesity, physical activity, family history of diabetes mellitus, type of diabetes, and duration of diabetes mellitus. But, the mean serum zinc level was significantly lower (P<0.01) for elderly diabetic subjects compared with adults and children. The mean serum zinc level for low social status (based on crowding index) patients was significantly lower (P<0.01), compared to the high social status patients. Significant difference was also noticed in mean ± SD values for serum zinc of good glycemic control and poor glycemic control of diabetics (p<0.01). The second part of the study showed that the mean value of serum triglycerides of the supplemented group decreased at the end of 90 days by 7.3%, whereas the mean values of serum zinc increased by 51.8%. In addition the mean values of serum glucose and HbA1c% of the supplemented group decreased by 6.6% and 5.9% respectively.

Conclusions Marginal zinc deficiencies were observed in the individuals studied with a higher prevalence in diabetic group. The measured zinc status is associated with the glycemic control of diabetes.

Duhok Med J 2011;5(2): 1-10.

Key words: Zinc status, Diabetes mellitus, Glycemic control

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Zinc is an essential element and necessary factor in a variety of enzymes. Alteration of zinc metabolism such as adequate zinc which is unavailable for these enzymes may contribute to the metabolic abnormalities.[1] Several studies suggested that lower dietary zinc intake and lower concentrations of serum zinc may contribute to diabetic complications. Hence, zinc supplementation may be deemed appropriate for diabetic patients.[2]

It is clear that the predominant effect on zinc homeostasis of diabetes is hypozincemia which may be the result of hyperzincuria or decreased gastrointestinal absorption of zinc or both.[3]

Despite evidence suggestive of possible widespread zinc deficiency in Iraqi population, attempts to assess zinc status in vulnerable groups to zinc depletion and low plasma zinc concentration have been few.[4,5] Thus, this preliminary study aimed to assess zinc status in patients with diabetes and to ascertain the relationship between zinc and glycemic control.

METHODS

This study was carried out on 206 diabetic patients and 156 apparently healthy subjects (control group) of comparable age and sex. The diabetic patients were recruited by consecutive sampling procedure from Duhok Diabetes Center. The controls were chosen from the relatives of patients attending Azadi Teaching Hospital during the period from September 2009 to June 2010.

A random sampling method was used to select a representative sample of diabetic patients registered in Duhok Diabetes Center (n=3678), and a total of 480 subjects living in Duhok city were then contacted by telephone and asked to take part in the study. After exclusion of 274 respondents who were newly diagnosed diabetes(less than one year duration of diabetes mellitus) and who had been supplemented with minerals, the remainders were enrolled in this study. Respondents were classified into two groups on the basis of insulin treatment. Insulin dependent (type1 DM, n=48) and non-insulin dependent (type2 DM, n=158), of these 117 were females and 89 were males aged 6-76 years.

A pre-tested questionnaire, designed to obtain information on gender, birth date, weight (recorded to the nearest kilogram using an electronic scale, height (recorded to the nearest centimeter using the CDC measuring board), waist circumference measured for each subject using tape measure, measuring blood pressure using mercuric sphygmomanometer, and their use of medications and minerals supplements, data on the number of house hold and number of rooms of the house, crowding index is an indicator for socioeconomic status and is calculated by dividing the number of household by the number of rooms of the house, data on duration of the DM recorded to the nearest one year, presence of any coexisting morbidities, family history of diabetes were also recorded.

The second part of the study was designed as a quasi experimental study with zinc supplementation in diabetic patients. All of the subjects who proved having low serum zinc levels, less than the cutoff value of marginal zinc deficiency (<70 µg/dl) were eligible for this study. Serum zinc concentrations at the time of pre-study were all within the range of (40-70 µg/dl). A protocol involving 28 subjects and 90 days supplementation period plus 15-day post supplementation was used to examine the relative response of serum zinc and metabolic components. The zinc-treated subjects were assigned to receive zinc gluconate tablets (AlHikmaa company/Jordan), Each tablet contains 20 mg of elemental zinc. Subjects were instructed to take one tablet twice a day. Of these 23 subjects completed the study presenting for the last visit.

Zinc deficiency has been identified depending on the determination of serum

zinc concentration in pre-breakfast serum zinc concentration from≤60 to ≤70 µg/dl and postprandial concentration of 10% lower than the pre-breakfast ones (55 µg/dl), are proposed cutoffs to indicate zinc deficiency.[6] The lowest value proposed by the WHO[7] for zinc is 50µg/dl, had been the most conservative, and was selected for this study as a cutoff for low serum zinc concentration. The prevalence of zinc deficiency in both genders and the relationship between zinc and glycemic control, duration of disease status, diabetes complications were also studied.

Marginal zinc deficiency and sub optimal zinc status in the subjects studied were evaluated according to the cutoff values of serum zinc stated by others.[8] Values between 50-70 µg/dl were considered marginal hypozincemia.

Blood samples were collected after overnight fasting for 12-14 hours. Blood samples for sera were collected in BD Vacutainer System CAT- plain tubes, and one ml was collected immediately into DMD-DISPO tubes containing K3 EDTA as anti coagulant for estimation of HbA1c. After 25-30 minutes, the serum was separated by centrifugation using a HITACHI centrifuge (model O5P-21) at 5000 rpm for 10 minutes.

The sera were then collected in a plain tube labeled numerically for later analysis. Then the serum for each one was processed immediately for measuring serum total cholesterol, triglycerides, HDL-C, glucose and creatinine by clinical chemistry analyzer Lisa. Xs (open, automated, discrete, random access).The sera were then stored at -80°C for later measurement of zinc and insulin levels.

Serum glucose, creatinine, total cholesterol and triglycerides were measured using direct enzymatic colorimetric method using commercial kits (biocode Hycel kit). HDL cholesterol was measured after precipitation with phosphotungestate mg^{+2} reagent combination solution. LDL cholesterol was calculated using Friedwald formula,[9] HbA1c% was estimated using commercial kit (Stanbio Glycohemoglobin Pre-Fil procedure No P350). Serum Insulin level was measured using ELISA technique (Accu-Bind ELISA microwells), monobind Inc. Lake forest, CA92630, USA. Insulin resistance was calculated using homeostasis model assessment of insulin resistance (HOMA-IR) by the equation:

HOMA.IR= [(FBG mg/dl)*0.05*insulin level µ IU/L] /22.5.

Zinc in serum and urine was measured by direct enzymatic colorimetric method, using a commercial kit (Giesse Diagnostic, Italy).

All data were analyzed using the Statistical Package for Social Science SPSS version 18.0; paired student t- test was used to assess differences in serum analyte among groups. Significance of association between various risk factors was assessed using Chi-square test. Level of statistical significance (P value) was set at < 0.05.

RESULTS

The prevalence of hypozincemia was 33.0% for the 362 individuals included in the study. The prevalence was significantly higher among diabetic patients than controls ($P<0.01$). This finding was still true even after the means of serum zinc were adjusted to marginal and severe hypozincemia. The mean ± SD values for serum zinc level of diabetic patients was 77.3± 22.1 µg/dl and the control group was 80.9 ± 15.6 µg/dl ($p<0.05$). The age and sex distribution was similar between individuals with diabetes and controls. No statistically significant difference was observed in hyperzincemia prevalence among groups (Table 1).

Serum zinc levels and the prevalence of hypozincemia according to related variables associated with diabetes mellitus are shown in table 2. Serum zinc level was lower in poor glycemic controls, but the difference was scant in absolute

Table 1. Zinc status in diabetic patients and controls

	Diabetic patients N=206	control N=156	P-value
Age (Years)*	43.3±9.1	41.2±7.5	NS
Male sex [n (%)]*	89(43.0	75(46.0)	NS
Serum zinc (µg/dl)*	77.3±22.1	80.9±15.6	< 0.05
Prevalence of hypozincemia [n (%)]	90(43.7)	31(19.9)	< 0.01
Prevalence of marginal hypozincemia [n (%)]	60(29.1	30(15.0)	< 0.01
Prevalence of severe hypozincemia [n (%)]	30(14.6)	1(0.7)	< 0.01
Prevalence of hyperzincemia [n (%)]	1(0.4)	2(1.3)	NS
Urinary zinc execration (ug/g Creatinine)*	84.4+19.4	77.0+10.0	< 0.05

**Results are mean ± SD*
NS: Not significant

Table 2. Mean+SD and the prevalence of serum zinc in diabetic patients according to some related variables

	N	Serum zinc levels (µg/dl)		zinc <70 µg/dl n (%)
		Mean	SD	
Poor glycemic control (HbA1c>7.6%)	89	73.6	27.2	36(40)*
Sedentary lifestyle	138	76.2	22.4	59(42.8)*
Diabetic complication	72	77.1	20.8	29(40.3)*
Hypertriglyceridemia >150 mg/dl	91	77.0	20.1	35(38.5)*
Low HDL-Ch <40 mg/dl	93	75.1	19.2	42(45.2)*
Hypercholesterolemia >200 mg/dl	62	74.8	18.7	29(46.8)*

** Not significant*

values and showed no statistical significance (F=0.257). According to current guidelines for zinc deficiency, which consider an individual hypozincemia when serum zinc level is lower than 70 µg/dl. This threshold was taken into account when marginal hypozincemia was assessed in the diabetic individuals, since clinical deficiency of the metal can be observed when serum zinc levels are lower than this value. Ninety of the 206 diabetic patient's analyzed presented values lower than normal zinc level, which represent a hypozincemia prevalence of 43.7%. No statistically significant difference was observed in hypozincemia prevalence related to poor glycemic, sedentary life style, diabetic complications, or lipid fractions.

We next used mean± SD and the p value to evaluate changes of zinc levels in relation to some epidemiological variables. However, no statistically significant effect was found using a P value of 0.05; for sex, BMI, central obesity, physical activity, family history of diabetes mellitus, type of diabetes, and duration of diabetes mellitus. The mean serum zinc level was significantly lower (P<0.01) for elderly diabetics (67.3 µg/dl, n=11) compared with adults and children (77.4 µg/dl, n=171 and 81.7 µg/dl, n=24) respectively. The mean serum zinc level for low social status (based on crowding index) individuals (74.6 µg/dl, n=64) was significantly lower (P<0.01), compared to

the high social status (80.2 µg/dl, n=142). Significant difference was noticed between mean ± SD values for serum zinc of good glycemic control and poor glycemic control of diabetics (Table 3).

Distribution of serum zinc level for children and adults are given in figures (1 and 2). Regarding diabetic individuals, children 33.3% had serum zinc values below the cutoff of 70 ug/dl suggests to be indicative of mild zinc deficiency,[7] compared with that of the adults 45.1%.

Table 3. Mean + SD and the P value of serum zinc levels in diabetic patients

	N	Serum zinc levels (µg/dl) Mean	SD	P value
Individuals				
Children	**24**	**80.7**	**24.1**	**<0.01**
Adults	**171**	**77.4**	**25.7**	
Elderly people	**11**	**67.3***	**18.3**	
Gender				
Males	**89**	**76.5**	**22.5**	**0.08**
Females	**117**	**77.9**	**21.7**	
BMI				
Normal	**65**	**77.2**	**19.7**	
Obese	**98**	**77.7**	**22.6**	
Central obesity				
Yes	**90**	**73.2**	**27.3**	**NS**
No	**116**	**76.8**	**22.2**	
Physical activity				
Physically active	**68**	**79.5**	**21.1**	**NS**
Sedentary lifestyle	**138**	**76.2**	**22.4**	
Social status				
Low (crowding index 3.6±2.1)	**64**	**74.6**	**22.9**	**< 0.01**
High (crowding index 3.3+1.9)	**142**	**80.2**	**22.2**	
Family history of diabetes				
Negative	**65**	**78.1**	**23.5**	**NS**
Positive	**141**	**76.9**	**21.3**	
Type of diabetes mellitus				
Type 1 DM	**48**	**75.4**	**20.5**	**NS**
Type 2 DM	**158**	**77.9**	**22.5**	
Glycemic control				
Good	**48**	**80.8**	**22.1**	**< 0.01**
Fair	**69**	**78.2**	**21.6**	
Poor	**89**	**72.6**	**22.0**	

NS means P is more than 0.05

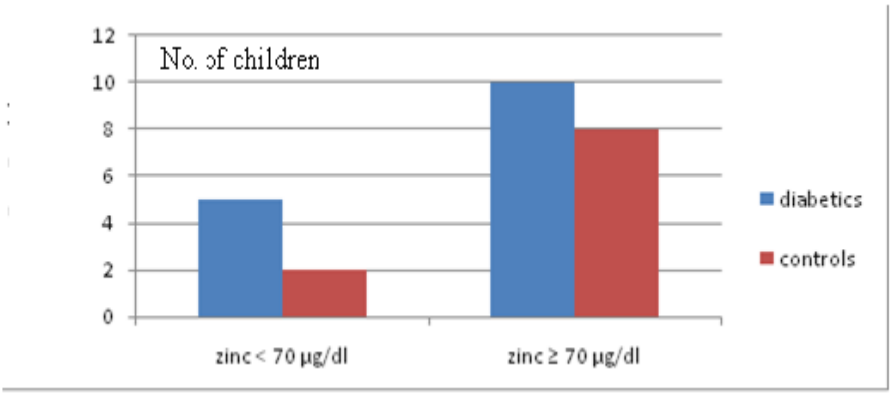

Figure 1. Distribution of serum zinc in children

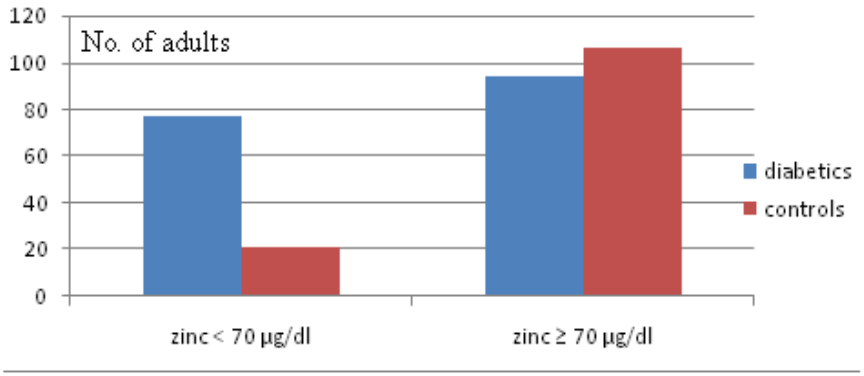

Figure 2. Distribution of serum zinc in adults

The second part of this study, which is an intervention trial, involved type 2 DM cases of whom; 28 were supplemented with oral zinc and followed for 90 days. The number of patients who completed the 90 days of follow up was 23. Table 4 shows the mean ± SD values for serum zinc level, FSG concentration, HbA1c% and lipid profile changes after 90 days of supplemented diabetics. The mean values of serum triglycerides of the supplemented group decreased at the end of 90 days by 7.3% (160.7 to 149.1), whereas the mean values of serum zinc increased by 51.8% (54.1 to 112.%), P <0.01 for all. In addition the mean values of serum glucose and HbA1c% of the supplemented group decreased by 6.6% and 5.9% respectively.

DISCUSSION

Marginal zinc deficiency appears to be an important public health problem in many developing countries, including Iraq.[10] In our sample of individuals included, marginal zinc deficiencies do exist, even among those without diabetes mellitus. For example, a high prevalence of zinc deficiency, defined as serum zinc less than 70 ug/dl was demonstrated in this study among diabetic patients and healthy controls, which markedly decline from 43.7% in diabetics to 19.9% in controls. Thus, a large group of diabetic patients may be at risk for developing zinc deficiency. It is noteworthy that 29.1% appear at risk for marginal zinc deficiency and 14.6% for severe zinc deficiency; important observations in biochemical zinc status during supplementation at physiological doses support the existence of zinc deficiency in those patients. The lower concentrations of serum zinc among those with diabetes mellitus may have resulted from lower intake, excessive loss or inherited disturbance in its metabolism.

Table 4. Changes in serum zinc level, FSG, lipid profile and HbA1c% after 90 days of follow up in the supplemented diabetic patients

Variable	Follow up diabetic group (n=23)			
	Baseline characteristic	90 days post Supplementation	Change of means	Percentage of change (%)
FSG (mg/dl)*	207.7±69.0	189.3±47.9	13.3	6.6
S. Creatinine (mg/dl)	0.76±0.13	0.75±0.13	0.01	1.3
Total cholesterol (mg/dl)	178.8±34.2	181.4±34.6	2.6	1.4
Triglycerides (mg/dl)*	160.7±69.7	149.1±40.4	11.6	7.3
HDL cholesterol (mg/dl)	44.3±12.0	44.7±13.1	-	-
LDL cholesterol (mg/dl)	101.0±22.7	104.8±30.9	-	-
HbA1c%*	7.25±1.04	6.82±0.79	0.43	5.9
Zinc (µg/dl)*	54.1±10.4	112.5±9.2	58.3	51.8
Insulin (µIU/L)	7.7±4.2	7.0±3.3	0.65	8.4
HOMA-IR	3.4	2.9	0.46	13.5

** P<0.05*
***P<0.01*
FSG (fasting serum glucose)
HDL (high density lipoprotein)
LDL (low density lipoprotein)
HOMA-IR (homeostasis model assessment of insulin resistance)

Our data show that individuals with diabetes mellitus excrete more zinc than those without this disease. Thus, the results of the present study suggest that excessive loss of zinc is an additive factor to low dietary bioavailability among patients with diabetes mellitus. A low plasma zinc concentrations and high urinary zinc excretion also has been observed.[11] However, it is likely that the changes in plasma and urinary zinc were caused solely by dietary imbalance i.e. the elderly diabetic patients had serum zinc values lower than that observed in elderly controls. This variation may in part relate to the defect in zinc absorption associated with hyperglycemia or diabetes. The decrease in GIT absorption, coupled with hyperzincuria may be aggravated in elderly diabetics and causes more hypozincemia. As well as low energy intake and poor dietary zinc consumption may be the cause.[12]

To rule out the influence of diabetic control on serum zinc status, mean serum zinc values were significantly lower in patients with poor glycemic control (based on blood HbA1c level) compared to the values in their counterpart from good glycemic control patients. This effect has been attributed to the more hyperzincuria in poor glycemic control patients.[13] Therefore, change in HbAIc% and glucose concentrations in the supplemented group of this study refers to the effective improvement in their glycemic control in response to zinc supplementation. In conclusion, a marked increase in serum zinc concentrations in the zinc treated diabetics appears to produce the restoration at least partially of zinc status and improvement of glycemic control. The effect of zinc has received great deal of interest. Through effects on glycemic control, zinc may decrease the risk of diabetic dyslipidemia. Larger prospective studies are needed to confirm our observations.

ACKNOWLEDGMENT

We would like to thank the staff of Duhok Diabetes Center especially Dr. Younis A.

Khalaf and Dr. Idress for their unlimited help and support.

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پوختە

ئاستێ کەرستێ زینکی لدەف نەخوشین شەکرێ

پێشەکی و ئارمانج: دیتنەکا گشتی لدەف نەخۆشین شەکرێ, جورێ ئیکێ و دووێ کیمبونا زینکیە دناف خوینێ دا. ئەگەرێن وێ یان بۆ زێدە ئیدرارا زینکیە یان ژی بۆ کێم مێزتنا ویە ژ لایێ رویڤیکان ڤە، یان ژی بۆ هەردو ئەگەران پێکڤە دزڤریت. ئەف کیمبونا جیبوی لهەمی لەشیدا جیدبیت ببیتە ئەگەر بو دیاربونا موزاعفاتین نەخوشیی. زبەر فێ جەندێ ئەف فەکولینە هاتە کرن بۆ هەلسەنگاندنا حالەتێ زینکی د ناڤ خوینێ دا ل دەڤ نەخۆشێن شەکرێ, وەکو هەولدانەك بو بیناسەکرنا نمونەیەکێ ژ نەخوشین شەکرێ ئەوین بیدڤ ب زینکی هەی. ئارمانج ئەوبو هەلسەنگاندنا حالەتێ زینکی د ناڤ خوینێ دا ل دەڤ نمونەیەکێ کو هاتبو هەلبژارتن بشیوەکێ عەشوائی ژ نەخۆشێن شەکرێ ل باژێرێ دهوکێ.

ریکێن ڤەکولینێ: داتا (بنگەهێ دهۆك یێ شەکرێ) ل پارێزگەها دهۆکێ/هەریما کوردستان/ عیراق د ماوەیێ دناڤبەرا چریا ئێکێ 2009 و خزیرانا 2010 هاتینە کۆمکرن. پارچەیا ئێکێ ژ ڤەکۆلینێ (362 cross sectional study) کەس بوون. 206 ژ وان نەخۆشێن شەکرێ بوون(جورێ ئیکێ 48 و جورێ دووێ 158 بوون)، یێن مایی 156 کەس بوون کو ب سەرڤە دساخلەمبوون. ل پارچەیا دووێ ژ ڤەکۆلینێ ((intervention study، 28 نەخۆشێن شەکرێ ژ جۆرێ دووێ هاتنە ژێگرتن ل دویڤ ساخلەتێن ژێگرتی، و رۆژانە 40 ملگم ژ ئەلەمێنتێ زینکی وەك شەکرکێن زینکی (zinc gluconate) بۆ ماوەیێ سێ هەیڤان ددانە وان، ژ وان ژی 23 نەخۆشان ئەڤ هەولدانە تمامکر. بیزانین هاتنە وەرکرتن ژهەر کەسەکی بریکا استبیانەکێ هاتبو جیکرن بو فێ فەکولینێ. ئاستێ شەکرێ دناف خوینیدا هاتە کیشان, بروفایلێ بەزی, HbA1c٪, و ئاستێ زینکی بوهەر کەسەکی.

ئەنجام: ریزا بەلافبونا کیمبونا زینکی دخوینیدا 33٪ ل 362 کەسین هاتینە هەلبزارتن دفێ فەکولینیدا. رێژەیا بەلاڤبوونا کێماتیا زینکی ب رەنگەکێ ئاشکرا زیدەتربو لدوف نەخوشین شەکرێ هەڤبەرکرن ل گەل کەسین ساخلەم (43.7 % vs 19.9%، p<0.01). بو هەلسەنگاندنا گهورینا د ئاستێ زینکیدا, دگەل هندێ چ کارتیکرنین ئاشکرا نەبون بکارئینانا 0.05 بو (p value) بو هەردوو رەگەزا, نیشاندەرێ کیشا لەشی, قەلەیوا نیڤا لەشی, چالاکیین فیزیائی, هەبونا نەخوشیا شەکرێ دناف مالیدا, جورێ نەخوشیا شەکرێ, و ماوێ نەخوشیی. بەلێ تیکرایێ ئاستێ زینکی د خوینیدا کیمتربوو ب رەنگەکێ ئاشکرا (P<0.01) ل دەڤ نەخوشین شەکرێ بین پیر هەڤبەرکرن ب جحیلا و زاروکان. بەلێ تیکرایێ ئاستێ زینکی د خوینیدا کیمتربوو ب رەنگەکێ ئاشکرا (P<0.01) ل دەڤ نەخوشین شەکرێ بین هەژار (ل سەر بناغەیێ نیشاندەرێ قەرەبالغێ) هەڤبەرکرن ب زەنگینا. جوداهیەکا ئاشکرا دیسا هەبو د تیکرایێ ئاستێ زینکی د خوینیدا ل دەڤ نەخوشین شەکرێ بین کونترلا وان یا شەکرێ یا باش هەڤبەرکرن ب وان بین کو کونترلا وان یا شەکرێ یا خراب(p<0.01). پارچەیا دووێ یا فەکولینێ دیارکر کو تیکرایێ ئاستێ بەزێ سیانی ل دەڤ وان کەسین کو زینك بو وان هاتیە دان هاتە خارێ ل دوماهیا90 روزا ب ریژا 7.3٪ بەلێ تیکرایێ ئاستێ زینکی بلندبو ب ریژا 51.8 ٪ دگەل هندێ تیکرایێ ئاستێ شەکرێ و HbA1c٪ دخوینا نەخوشین کو زینك بو هاتیە دان هاتە خارێ ب ریژا 6.6٪ و 5.9٪ ل دیف ئیك.

دەرئەنجام: کیمبونا زینکی هاتە دیتن لدەف ئەو کەسین دفێ فەکولینێ دا دگەل ریژەکا بەلافبونێ یا پتر دنەخوشین شەکریدا. ئاستێ زینکی بێ کیشایی پەیوەندی یا هەی دگەل کونترلکرنا شەکرێ یا نەخوشیا شەکرێ.

الخلاصة

حالة الخارصين لدى مرضى السكري

خلفية واهداف البحث: كمعاينه عامه لداء السكري, النوع الاول وبالاضافه الى النوع الثاني هو نقص الخارصين في الدم نتيجة أما الى كثرة تدرر الخارصين او نقص أمتصاصها عن طريق الامعاء او الاثنين معا. النقص للخارصين في عامه الجسم قد يكون السبب لظهور مضاعفات المرض. ولذلك' تمت هذه الدراسه لتقييم حاله الخارصين في مرضى السكري' في محاوله لتعريف عينه مرضى السكري لمن هم بحاجه الى اعطائهم الخارصين. الهدف كان لتقييم حالة الخارصين في الدم في عينة مختاره عشوائيا لمرضى السكري في مدينه دهوك.

طرق البحث: تمت جمع البيانات ما بين الفترة من تشرين الاول 2009 و حزيران 2010 في مركز دهوك للسكري في محافظة دهوك/أقليم كردستان/العراق. تضمن الجزء الاول من الدراسة(362 (cross sectional study شخص. بينهم 206 مصابون بمرض السكري(النوع الاول, عدد 48; النوع الثاني، عدد 158) والاخرين كانوا 156 اشخاص اصحاء ظاهريا. في الجزء الثاني من الدراسة (intervention study)، تم اختيار 28 مريض سكري من النوع الثاني حسب الصفات المختارة وتم اعطائهم 40 ملغم من عنصر الخارصين كسكرات الخارصين (zinc gluconate) كل يوم لمدة ثلاثة أشهر, ومنهم 23 مريض كملوا المحاولة. تم اخذ معلومات عامه من كل شخص عن طريق استبيان صمم خصيصا لهذه الدراسه. تم قياس مستوى السكر في الدم' ملف الدهون و HbA1c ومستوى الخارصين لكل شخص.

النتائج: نسبه انتشار نقص الخارصين في الدم كان 33.0% لل 362 شخص تضمنوا في هذه الدراسه. نسبه انتشار النقص كان أعلى بشكل ملحوظ في مرضى السكري مقارنه بالأشخاص الأصحاء (43.7 vs 19.9%، p<0.01). لتقييم التغيرات في مستويات الخارصين, علاقة ببعض المتغيرات. مع ذلك لم يتواجد أي تأثير ملحوظ باستعمال 0.05 للقيمه P)) للجنس و مؤشر كتله الجسم و البدانة ألوسطيه'النشاطات الفيزيائيه' وجود مرض السكري في سجل العائله و نوع مرض السكري و فترة المرض. ولكن معدل القيمة لمستوى الخارصين في الدم كان اقل بشكل ملحوظ(p<0.01) في مرضى السكري المسنون مقارنه مع ألأشخاص البالغين وألاطفال. معدل القيمة لمستوى الخارصين في الدم كان اقل بشكل ملحوظ(p<0.01) في ألأشخاص ذوي الطبقة الفقيرة (اعتمادا على مؤشر الازدحام) مقارنة للاشخاص ذوي الطبقة الغنية. اختلاف ملحوظ وجد أيضا في معدل القيم لمستوى الخارصين في الدم في مرضى السكري من ذوي السيطرة السكرية الجيدة والسيطرة السكرية السيئة (p<0.01) . الجزء الثاني من الدراسة أظهرت بأن معدل القيمة لمستوى الشحوم الثلاثية في الدم للأشخاص الذين تم إعطاءهم الخارصين انخفضت في نهاية اليوم التسعون بنسبة7.3% بينما معدل القيمة لمستوى الخارصين في الدم ارتفع بنسبة 51.8%. بألأظافه إلى أن معدل ألقيمه لمستوى السكر و HbA1c% في الدم للأشخاص الذين تم إعطاءهم الخارصين انخفضت بنسبة 6.6% و 5.9% بالتسلسل.

الاستنتاجات: نقص ألخارصين الحافي تم مشاهدته في الاشخاص المشمولين في هذه الدراسه مع نسبه انتشار اكثر في عينة مرضى السكري. حاله الخارصين المقاسه لها علاقه مع السيطرة السكريه لمرض السكري.

ROLE OF CHROMOGRANIN A IN THE ASSESSMENT OF SYMPATHETIC ACTIVITY IN ACUTE MYOCARDIAL INFARCTION

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Submitted 14 May 2011; accepted 1 Oct 2011

ABSTRACT

Background and objectives Measurement of chromogranin A in plasma has been used for the diagnosis and prognosis of many endocrine and neuroendocrine tumors that are associated with increased catecholamines secretion. Little is known, however, about the magnitude of increased sympathetic activity after acute myocardial infarction. Investigating the value of plasma chromogranin A as a quantitative measurement for this purpose probably will be of clinical significance. The objective was to evaluate the sympathetic nervous system activity in patients with acute myocardial infarction by measuring plasma chromogrnin A.

Methods This study involved 45 patients with acute myocardial infarction and 30 apparently healthy subjects as controls. Serum troponin I and CK-MB were measured by VIDAS machine and kinetic method respectively, chromogranin A was measured by ELISA technique.

Results Plasma chromogranin A in myocardial infarction patients (307.4 ng/ml) was significantly higher ($p< 0.001$) than that in controls (182.6 ng/ml). The value of plasma chromogranin A level (≥ 252.1 ng/ml) had an accuracy of 77.3 %, sensitivity of 64.4 % and 96.7 % specificity for establishing increased sympathetic system activity in patients with acute myocardial infarction. Patients with acute inferior wall myocardial infarction showed no appreciable difference in plasma chromogranin A level (308.1 ng/ml) from patients with other sites of myocardial wall infarction (306.8 ng/ml). Sympathetic activity was significantly lower in myocardial infarction patients who received morphine compared to those with negative history of morphine administration (236 vs 325.2 ng/ml, respectively, $p = 0.01$). However, plasma chromogranin A level was not influenced by gender, history of diabetes mellitus and smoking history.

Conclusions Measurement of plasma chromogranin A level is valuable for evaluating sympathetic activity after acute myocardial infarction. The magnitude of increased sympathetic system activity is not different in patients with acute inferior wall myocardial infarction and patients with other sites of myocardial wall infarction. In addition, morphine administration modulates sympathetic system activity after acute myocardial infarction.

Duhok Med J 2011;5(2): 11-23.

Key words: Chromogranin A, Sympathetic activity, Acute myocardial infarction

Acute myocardial infarction (MI) is a medical condition characterized by damage and potential death (necrosis) of cardiac myocytes caused by prolonged interruption of the blood supply to a part of the heart and it is the leading cause of death both for men and women.[1,2]

Decreased cardiac output in acute MI

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lead to activation of several neurohormonal systems such as renin-angiotensin-aldosterone system, release of anti-diuretic hormone, secretion of atrial natriuretic peptides and activation of sympathetic nervous system.[2,3]

Neurons and cells of the neuroendocrine system contain vesicles which store and release a variety of peptide hormones, biogenic amines and neurotransmitters. Chromogranins and secretogranins are a unique group of acidic, soluble secretory proteins found in vesicles of neurons and neuroendocrine cells. There are three types of chromogranins; the first one is chromogranin A (Cg A), a 49 kDa which consists of 439 amino acids residues, first isolated from chromaffin cells of the adrenal medulla. The second type is chromogranin B (Cg B) that consists of 657 amino acids, and initially characterized in a rat pheochromocytoma cell line. The third chromogranin is secretogranin II (chromogranin C), which is isolated from the anterior pituitary gland.[4]

In granulated vesicles of sympathetic postganglionic neurons and adrenal medullary cells, norepinephrine and epinephrine are bound to adenosine tri-phosphate and associated with chromogranin A.[5]

Chromogranin A increase has been proposed as a diagnostic marker of several neuroendocrine tumors such as pheochromocytoma,[6] parathyroid adenoma,[7] carcinoid tumors,[8] pancreatic islet-cell and aortic body tumours.[9] In addition to that, measurement of chromogranin A has yielded new insights into the pathogenesis of essential hypertension.[4]

Circulating levels of chromogranin A appear to be a better index of sympathetic activity.[5] It has been reported that serum concentration of chromogranin A increases after cardiac arrest, strenuous exercise and hypoglycaemia.[10]

As far as we are aware, data concerning the measurement of chromogranins, particularly chromogranin A in apparently healthy subjects and in diseased conditions, are not available in our locality. Little information, however, are available concerning the role of chromogranin A in the assessment of sympathetic system activity in cardiovascular disorders.

The current study aims to contribute whether and to what extent the measurement of plasma chromogranin A level can be used for the assessment of sympathetic activity in patients with AMI.

METHODS

Subjects included in this study were classified into two groups: patients with acute MI (n = 45, comprised 39 males and 6 females, their average age = 57.62 years) and a group of apparently healthy subjects (n = 30, among them 25 were males and 5 females, their average age = 46.63 years). General information and history were reported, then measurement of vital signs, echocardiography parameters (ejection fraction and fractional shortening), then venous blood samples were obtained for measurement of plasma concentration of chromogranin A, serum concentrations of cardiac biomarkers (troponin I and CK-MB) and high sensitivity C-reactive protein.

In MI group, blood samples were obtained within 24 hours of the onset of symptoms and centrifuged at 3000 g for 30 min. at 4 ^{o}C. The serum and plasma were obtained and frozen at -28 ^{o}C until the time of analysis.

Control subjects were asked to fast overnight (10 – 12 hours). Next day at 9 a.m. the questionnaire was completed and sampling started. One subject was investigated each day. All apparently normal volunteers were kept in a calm place at (20-25 ^{o}C) and in lying position for 30 minutes before withdrawing blood

samples. Blood samples were taken in the same way as performed for patient group.

Plasma chromogranin A levels were measured by ELISA using Epitope Diagnostics, Inc. (EDI™) kit, serum cardiac troponin I measured by VIDAS using BioMerieux® SA, France kit. Serum CK-MB measured by CK-MB isoenzyme immunoinhibition method using BIOLABO SA, France kit and hs-CRP measured by ELISA using Monobind Inc., USA kit.

RESULTS

There was a highly significant increase (P < 0.001) of mean plasma chromogranin A level in MI cases (307.4±19.43 ng/ml) compared to the control group (182.6±9.59 ng/ml) (Figure 1).

There were statistically significant increases in the serum levels of CK-MB (101 vs 13.7 UI/L, p< 0.001), troponin I (3.9 vs 0.01 µg/L, p < 0.001) and high sensitivity C-reactive protein (7.3 vs 2.8 µg/ml, p < 0.002) in the MI group compared to the controls as shown in table 1.

Using receiver operating characteristics (ROC) curve, table 2 and figure 2 illustrate that serum troponin I was of highest validity in differentiating MI from healthy subjects with an area under the curve (AUC) of 0.933, followed by CK-MB (AUC = 0.905) and plasma chromogranin A (AUC = 0.817) respectively, hs-CRP was of the lowest validity (AUC = 0.713) among the selected parameters for differentiating MI cases from controls.

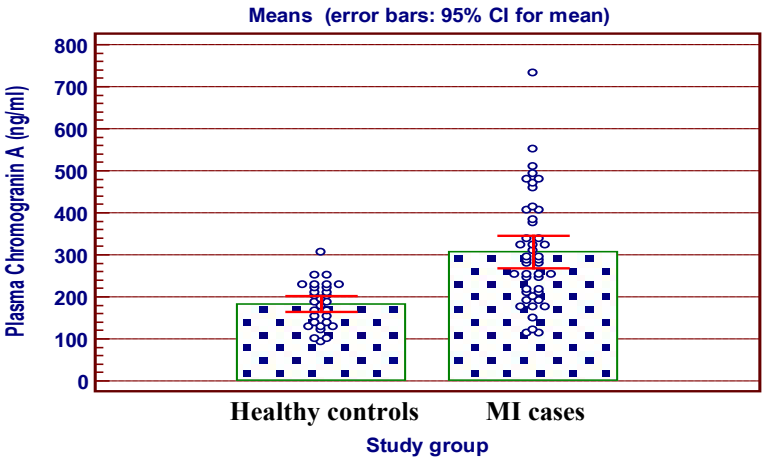

Figure 1. Comparison of the mean plasma Chromogranin A between MI cases and healthy controls

Table 1. Measurements of serum cardiac biomarkers and high sensitivity C-Reactive Protein in the studied groups

Parameters	Healthy controls N = 30	MI N = 45	P value
Serum CK-MB (UI/L)			
Mean ± SE	**13.7 ± 0.62**	**101 ± 12.22**	**<0.001***
Serum Troponin-I (ug/L)			
Median	**0.01**	**3.9**	**<0.001****
Interquartile range	**(0.01 - 0.01)**	**(0.5 - 14.95)**	
High sensitivity C-Reactive Protein (ug/ml)			
Median	**2.8**	**7.3**	**0.002****
Interquartile range	**(1.6 - 5.1)**	**(2.9 - 13.6)**	

** Independent samples t-test was used*
*** Mann-Whitney U-test was used*

Table 2. ROC area for plasma chromogranin A and selected cardiac biomarkers when used in differentiating MI cases from healthy controls

Parameters	ROC area	P
Plasma Chromogranin A (ng/ml)	0.817	<0.001
Serum Troponin-I (ug/L)	0.933	<0.001
Serum CK-MB (UI/L)	0.905	<0.001
High sensitivity C-Reactive Protein (ug/ml)	0.713	0.002

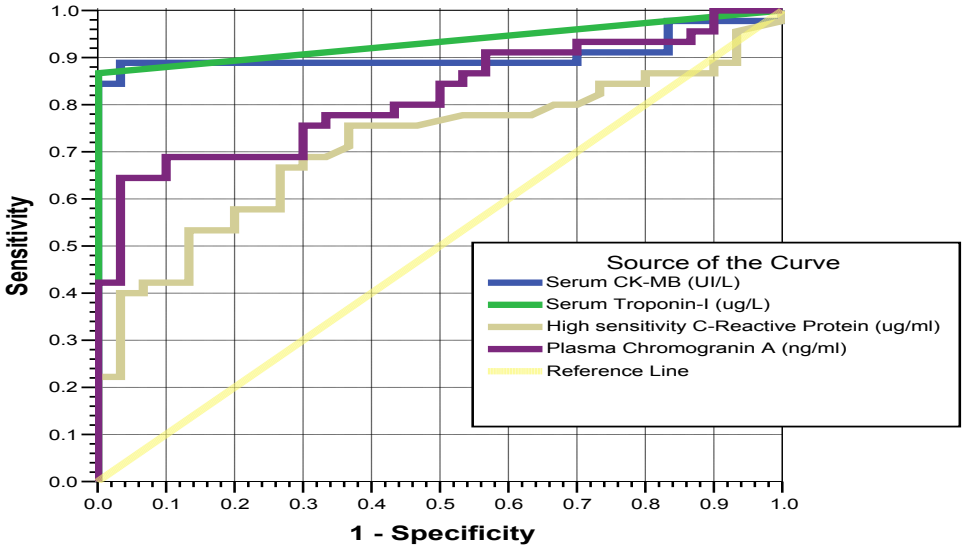

Figure 2. ROC curve showing the trade-off between sensitivity (true positive) and 1-specificity (false positive) for plasma chromogranin A and selected cardiac biomarkers when used in differentiating acute MI patients from healthy controls

Plasma chromogranin A cut-off value associated with highest sensitivity is positive if ≥ 107.7 ng/ml, which is associated with detection rate (100 %) for diagnosis and increased sympathetic activity in acute MI cases when used for screening purposes. A subject, who is negative for the test at this cut-off value, is considered negative for acute MI and increased sympathetic system activity with 100 % certainty level.

The optimum (typical cut-off value) is (252.1 ng/ml) which yields a sensitivity of (64.4 %), accuracy (77.3%) and (96.7 %) specificity. Testing positive at this cut-off value will establish the diagnosis and increased sympathetic system activation in MI with 95.1 % confidence. In the same context, testing negative will exclude MI and sympathetic overactivity in MI with (96.1 %) confidence. The cut-off value of the highest specificity is 307.5 fmol/ml. At this cut-off value, the diagnosis and increased sympathetic system activation in MI is established with 100 % confidence (Table 3).

Plasma chromogranin A reached to its highest level after 13 hours from onset of symptoms (345.7 ng/ml), but it was statistically not different from other subgroups (when blood sampling done within 12 hours of the onset of symptoms) (p = 0.29) (Figure 3).

Thrombolytic therapy induced appreciable but statistically not significant decrease of plasma chromogranin A level compared to those with negative history of thrombolytic therapy (276 vs 340.2 ng/ml, p = 0.1). However, patients with positive history of thrombolytic therapy showed significantly higher levels of serum troponin I (Table 4).

Table 3. Validity parameters of plasma chromogranin A, selected cardiac biomarkers and high sensitivity C-reactive protein when used to differentiate MI from controls

Parameters	Sensitivity	Specificity	Accuracy	PPV at pretest probability		*NPV at pretest probability =10%*
				50%	90%	
Positive if greater than or equal to cut-off value						
Plasma chromogranin A (ng/ml)						
107.7 (highest sensitivity)	**100.0**	**10.0**	**64.0**	**52.6**	**90.9**	***100.0***
252.1 (Optimum)	**64.4**	**96.7**	**77.3**	**95.1**	**99.4**	***96.1***
307.5 (highest specificity)	**42.2**	**100.0**	**65.3**	**100.0**	**100.0**	***94.0***
Serum Troponin I (µg/L)						
0.01 (Opimum, highest sensitivity and highest specificity)	**86.7**	**100.0**	**92.0**	**100.0**	**100.0**	***98.5***
Serum CK-MB (UI/L)						
10.0 (highest sensitivity)	**97.8**	**16.7**	**65.4**	**54.0**	**91.4**	***98.6***
18.9 (Optimum cut-off)	**88.9**	**96.7**	**92.0**	**96.4**	**99.6**	***98.7***
23.3 (Highest specificity)	**84.4**	**100.0**	**90.6**	**100.0**	**100.0**	***98.3***
High sensitivity C-Reaction Protien (µg/ml)						
0.5 (highest sensitivity)	**95.6**	**6.7**	**60.0**	**50.6**	**90.2**	***93.2***
2.95 (Optimum)	**75.6**	**63.3**	**70.7**	**67.3**	**94.9**	***95.9***
14.90 (highest specificity)	***22.2***	***100.0***	***53.3***	***100.0***	***100.0***	***92.0***

PPV is positive predictive value
NPV is negative predictive value

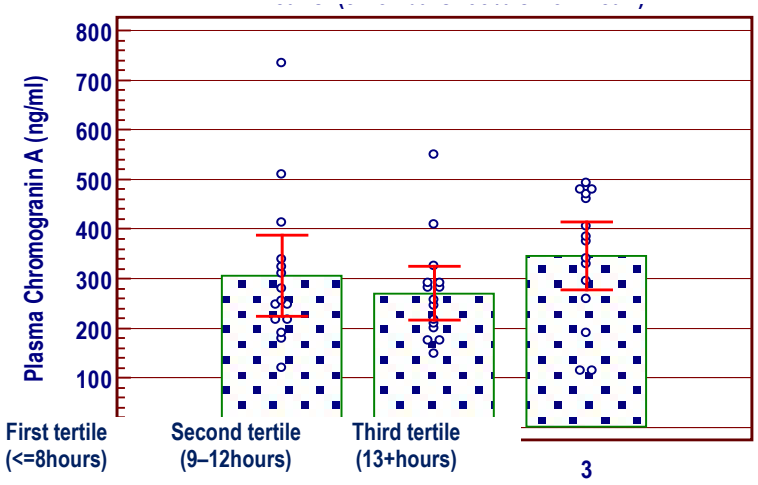

Figure 3. Showing the mean plasma Chromogranin A by ordered categories of time interval between onset of symptoms and blood sampling in patients with acute myocardial infarction

Table 4. Comparison of the plasma chromogranin A and selected serum cardiac biomarkers in MI patients with positive and negative history of thrombolytic therapy

Parameters	Received Thrombolytic therapy (Actilyse)		P
	Negative N = 22	Positive N = 23	
Plasma Chromogranin A (ng/ml)			
Mean ± SE	**340.2 ± 31.03**	**276 ± 22.5**	**0.1*[NS]**
Serum CK-MB (UI/L)			
Mean ± SE	**78.4 ± 14.39**	**122.6 ± 18.76**	**0.07*[NS]**
Serum Troponin-I (ug/L)			
Median	**1.39**	**9.58**	**0.029****
Interquartile range	**(0.16 - 6.77)**	**(1.11 - 86.9)**	
High sensitivity C-Reactive Protein (ug/ml)			
Median	**5.2**	**10.7**	**0.06**[NS]**
Interquartile range	**(1.9 - 8.6)**	**(3.2 - 20.1)**	

* *Independent samples t-test was used*
** *mann-Whitney U-test was used*

No statistically significant differences in plasma chromogranin A levels (Table 5) and other selected cardiac biomarkers were noticed among patients with inferior wall MI and other sites of myocardial wall infarction.

Measurement of echocardiography parameters and vital signs showed no significant or appreciable differences between patients with inferior wall and other sites of MI (Data are not shown).

As shown in table 6, the mean plasma chromogranin A level was significantly (p = 0.01) lower among patients with acute MI who received morphine (325.2 ng/ml) on admission, compared to those who did not receive morphine (236 ng/ml). Meanwhile, other independent variables (patient's history of CVD, family history of CVD, history of diabetes mellitus and gender) did not influence an appreciable and significant difference in plasma chromogranin A levels.

Table 5. Comparison of plasma chromogranin A, selected serum cardiac biomarkers and high sensitivity C-reactive protein among patients with inferior wall MI and other sites of myocardial wall infarction

Parameters	Site of MI		P
	Inferior wall N = 25	Other sites N = 20	
Plasma Chromogranin A (ng/ml)			
Mean ± SE	**306.8 ± 23.55**	**308.1 ± 33.03**	**0.98*[NS]**
Serum CK-MB (UI/L)			
Mean ± SE	**94.5 ± 16.47**	**109.1 ± 18.54**	**0.56*[NS]**
Serum Troponin-I (ug/L)			
Median	**2.95**	**3.95**	**0.6**[NS]**
Interquartile range	**(0.5 - 10.8)**	**(0.47 - 25.95)**	
High sensitivity C-Reactive Protein (ug/ml)			
Median	**10.4**	**4.8**	**0.21**[NS]**
Interquartile range	**(3.2 - 14.9)**	**(2.9 - 12.1)**	

* *Independent samples t-test was used*
** *Mann-Whitney U-test was used*

Table 6. The mean plasma Chromogranin-A by selected independent variables among cases with MI

Independent variables	Plasma Chromogranin A (ng/ml)		P (t-test)
	Mean ± SE	N	
Patient's history of CVD			**0.35[NS]**
Negative	283.1 ± 26.4	13	
Positive	317.2 ± 25.1	32	
Family history of CVD			**0.68[NS]**
Negative	300.4 ± 24.4	26	
Positive	361.9 ± 32.3	19	
History of diabetes mellitus			**0.34[NS]**
Negative	295.5 ± 21.37	34	
Positive	344.1 ± 44.27	11	
Received morphine			**0.01**
Negative	325.2 ± 22.63	36	
Positive	236 ± 24.99	9	
Sex			**0.95 [NS]**
Female	303.5 ± 66.1	6	
Male	308 ± 20.39	39	

According to the smoking history, each study group was divided into three subgroups; non smoker, current smoker and X-smoker. In the control group, no significant difference were noticed in the levels of plasma chromogranin A and cardiac biomarkers between the subgroups (Data are not shown).

Meanwhile, in the MI group significantly higher levels of CK-MB and troponin I were observed in the current smokers compared to non smokers and X-smokers (133.1 vs 72.7 and 64.7 UI/L, p = 0.032) and (10.8 vs 1.12 and 0.17, p = 0.001) respectively (Table 7), but, plasma chromogranin A and serum hs-CRP levels were not significantly affected by smoking history.

Table 7. Measurement of plasma chromogranin A, serum cardiac biomarkers and high sensitivity C-reactive protein in MI cases according to smoking history

MI cases	Smoking history			P value
	Non smoker N = 16	Current smoker N = 22	X-smoker N = 7	
Plasma Chromogranin A (ng/ml)				
Mean ± SE	353.7 ± 40.61	272 ± 20.88	312.6 ± 45.86	0.16*[NS]
Serum CK-MB (UI/L)				
Mean ± SE	72.7 ± 16.05	133.1 ± 18.32	64.7 ± 28.52	0.032*
Serum Troponin-I (ug/L)				
Median	1.12	10.8	0.17	0.001**
Interquartile range	(0.03 - 7.3)	(2.63 - 82.25)	(0.01 - 2.64)	
High sensitivity C-Reactive Protein (ug/ml)				
Median	6.6	8.2	3.1	0.29**[NS]
Interquartile range	(2 - 21.2)	(4.1 - 11.1)	(1.7 - 7.8)	

** One-way ANOVA test was used*
***Kruskall-Wallis test was used*

DISCUSSION

Significant increases in serum troponin I and CK-MB were observed in patients with acute myocardial infarction compared to the controls. These markers are specific for myocardial cell damage[11] and support our clinical diagnosis of acute myocardial infarction.

Patients with acute myocardial infarction had an increased plasma chromogranin A level about 1.7 fold in comparison to normal controls. Although limited data are available in this field, our findings are consistent with those of other studies[12, 13] and indicate that sympathetic system activity is greater in patients with acute myocardial infarction than the normal subjects.

The present study showed that an optimum (typical) cut-off value of more than or equal to 252.1 ng/ml had an accuracy of 77.3 %, sensitivity of 64.4 % and 96.7 % specificity for establishing increased sympathetic activity in acute myocardial infarction.

Moreover, recent information demonstrated that chromogranin A is detected in human myocardial secretory granules containing atrial natriuretic peptide, and myocardial production of chromogranin A in humans is enhanced in patients with dilated and hypertrophic cardiomyopathy,[12] suggesting that chromogranin A may be released from the myocardium in conditions characterized by increased pressure or volume overload.

Therefore, determination of plasma chromogranin A is clinically significant and might be of value in the diagnosis of acute myocardial infarction (in addition to the assessment of sympathetic system activity) which can be used as an additional new biochemical marker for the diagnosis of acute myocardial infarction. However, this does not rule out the possibility that other organs, including adrenal glands, might be the contributing sources to increased levels of chromogranin A.[13]

This study showed that sympathetic hyperactivity is not affected by the time span after acute myocardial infarction, indicating that the magnitude and the duration of this activation are probably linked to the extent of myocardial injury and the degree of ventricular dysfunction. Our results are in agreement with an experimental study carried out by Jardine et al.[14] who reported a sustained increase in sympathetic system activity following experimental myocardial infarction.

Patients with positive history of thrombolytic therapy had plasma chromogranin A level about 19 % lower than in patients with negative history of thrombolytic therapy. Although this difference was statistically not significant, this effect of thrombolytic therapy on sympathetic system activity might partly contribute to the hemodynamic stability of patients with acute myocardial infarction following reperfusion therapy.

Patients with positive history of reperfusion therapy showed higher serum levels of cardiac biomarkers compared to those with negative history of such therapy. This might indicate that restoration of blood flow to an ischemic area (or necrotic area) of myocardial wall cause washing of large quantities of these cardiac biomarkers into the circulation. In addition, troponin I is more abundant in the myocardium than CK-MB,[15,16] which might contribute to the more obvious elevation of troponin I following thrombolytic therapy.

Our study showed no influence of site of infarction on levels of plasma chromogranin A. Indicating that the degree of sympathetic system activation is more or less similar and not dependent on the site of infarction.

We found that morphine administration significantly decreases sympathetic system activity after acute MI. Our results are consistent with those reported by Takashi et al.[17] and Kienbaum et al.[18] On the other hand, this finding is not consistent with results observed by

Mildh et al.[19] and Carter et al.[20] who demonstrated an increased sympathetic activity and mean arterial pressure after morphine administration.

The mechanism through which morphine decrease the sympathetic activity could be the binding of morphine to opioid receptors of sympathetic centers in the brain stem and spinal cord.[21]

It has been found that co-release of chromogranin A and catecholamine is increased in smokers.[22] However, we found in the present work that smoking does not influence chromogranin A levels neither in the control subjects nor in patients with acute myocardial infarction. This might be attributed to desensitization and downgrading of nicotinic receptors at autonomic ganglia due to chronic excessive exposure to nicotine, because majority of smokers in this study (71.4%) were moderate and heavy smokers.

Current smokers in the myocardial infarction group showed significantly higher serum levels of cardiac biomarkers. This indicates that current smokers are liable to a more extensive damage of myocardial wall during such attacks than non smokers or X-smokers. This could be attributed to higher plasma fibrinogen level in the current smokers.[23] Plasma fibrinogen levels show a dose dependent increase in smokers, and abstention from smoking reduces both synthesis and plasma fibrinogen level.[24] high plasma fibrinogen levels promote atherogenesis, thrombogenesis and increased blood viscosity with consequent extensive occlusion of coronary arteries.[25]

In agreement with previous studies, [3,26,27] we found that hs-CRP is significantly increased in acute myocardial infarction. High values of hs-CRP suggest that the patient may be at increased risk of cardiac events[28]; therefore, patients with acute myocardial infarction should be kept under strict medical observation within the first few days.

Patients with positive history of thrombolytic therapy showed significantly higher levels of hs-CRP than those with negative history. This indicates that restoration of blood flow to a damaged tissue will consequently activate the inflammatory process.

We conclude that these data indicate that AMI is associated with increased sympathetic nervous system activity and measurement of plasma chromogranin A levels can be used readily to assess the extent of this activity.The magnitude of increased sympathetic system activity is not different in patients with acute inferior wall MI and patients with other sites of myocardial wall infarction. Morphine administration modulates sympathetic system activity after AMI. Increased sympathetic system activity after AMI is not restricted to a certain period of time, and is attributed to the degree of hemodynamic stability following such attacks. Sympathetic system activity is not increased in heavy smokers which is most likely due to down-regulation and desensitization of nicotinic receptors at autonomic ganglia following long-term exposure to nicotine. As well as high sensitivity C-reactive protein level peaks after 12 hours of the onset of AMI, during which the patient is at increased risk of complications and careful observation is needed until hs-CRP begins to decrease.

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پوخته

رولێ کروموکرانین ئەی د هەلسەنگاندنا چالاکیا سیستەمێ سمپاتتیك دا پشتی ئەنفارکشنا دلی یا دژوار

پێشەکی و ئارمانج: دیارکرنا ریژا Chromogranin A دناڤ پلازمایێ دا یا هاتییە بکارئینان بۆ دەسنیشانکرن و پێشبینکرنا پەنجەشێرێن دەمارەخانا و رژێنێن گرتی ئەوێن گرێدای برژاندنا catecholamine ڤە دناڤ خویناڤێدا. کێم پێزانین بێت هەین لسەر چەندایەتیا زێدەبونا چالاکیا سیستەمێ سمپاتتیك پشتی پەیدابونا ئەنفارکشنا دلی، دیڤچۆنا بهایێ Chromogranin A دناڤ پلازمایێدا وەك پیڤەرەکێ چەندایەتی بۆ ڤێ مەرەمێ رەنگە گرنگیەکا کلینیکی هەبیت. ئارمانجا ڤەکولینێ هەلسەنگاندنا چالاکیا سیستەمێ سمپاتتیك پشتی ئەنفارکشنا دلی یا دژوار بریکەکا چەندایەتی بپیڤانا ئاستێ Chromogranin A دناڤ پلازمایێ دا.

ریکێن ڤەکولینێ: ئەڤ ڤەکولینە ژ دوو گروپا پێك دهات: 45 نەخوشێن ئەنفارکشنا دلی یا دژوار و 30 مرۆڤێن سروشتی. فورما پێزانینا بۆ هەردوو گروپا هاتە پڕکرن. ریژا Chromogranin A دناڤ پلازمایێدا و پێکهاتێن بایو کیمیاوی بێن مرنا ماسۆلکا دلی هاتنە دیارکرن. د گروپێ ئەنفارکشنێ دا نمونێن خوینێ هاتنە وەرگرتن دماوێ 24 دەمژمێرادا ژ دەسپێکا پەیدابونا نیشانێن نەخوشیێ.

ئەنجام: هوسا دیاربو زێدەبونا مەعنەوی د ریژا Chromogranin A دناڤ پلازمایێ دا لدەف نەخوشێن ئەنفارکشنێ (307.4 Vs 182.6 ng/ml, P < 0.001) دناڤ هەردوو گروپاندا. ریژا ئاستێ Chromogranin A دناڤ پلازمایێ دا پتر ژ 252.1 ng/ml شیایە زێدەبونا چالاکیا سیستەمێ سمپاتتیك دیاربکەت بریژا 77.3٪ بهویراتی، 64.4٪ هەستداری و 96.7٪ تایبەتمەندی لدەف نەخوشێن ئەنفارکشنێ. هیچ جیاوازی دناڤبەرا ئەنفارکشنا دلی ژ جورێ inferior و ئەنفارکشنا جهێن دی ژ دیوارێ دلی دیارنەبوویە (306.8 Vs 308.1 ng/ml) لدیفئێکدا، دگەلدا هیچ جیاوازی یا مەعنەوی د چالاکیێن زیندەکیدا دیارنەبوویە دناڤبەرا ڤان هەردوو گرۆپاندا. کێمبوونەکا مەعنەوی د چالاکیا سیستەمێ سمپاتتیکدا (بنوینەراتیا ئاستێ Chromogranin A دناڤ پلازمایێ دا) دیارکریە لدەف نەخوشێن ئەنفارکشنا دلی ئەوێن مورفین وەرگرتین بەرەوردکرن دگەل وان نەخوشان ئەوێن مورفین نەوەرگرتین (236 Vs 325.2 ng/ml, P = 0.01) لدیفئێکدا. هەرچەندە رەگەز، نەخوشیا شەکرێ و جگارە کێشانێ هیچ کارتێکرن نەبوویە لسەر ئاستێ Chromogranin A دناڤ پلازمایێ دا.

دەرئەنجام: ئەڤ داتایە زێدەبوونا چالاکیا سیستەمێ سمپاتتیك پشتی ئەنفارکشنا دلی دیاردکەن، و پشکنینا ئاستێ Chromogranin A دناڤ پلازمایێ دا رەنگە بێتە بکارئینان بۆ هەلسەنگاندنا ڤێ چالاکیێ. چەندایەتیا زێدەبوونا چالاکیا سیستەمێ سمپاتتیك دناڤبەرا ئەنفارکشنا دلی ژ جورێ inferior و ئەنفارکشنا جهێن دی ژ دیوارێ دلی وەکی ئێکە. وەرگرتنا مورفینی، بەرسڤدانەڤەیا سیستەمێ سمپاتتیك دگوهوریت پشتی ئەنفارکشنا دلی یا دژوار.

الخلاصة

دور الكروموكرانين أي في تقدير نشاط الجهاز العصبي الودي في احتشاء العضلة القلبية الحاد

خلفية واهداف البحث: إستعمل قياس ال chromogranin Aفي البلازما في تشخيص العديد من أورام الغدد الصم و الغدد الافرازية (neuroendocrine) التي تفرز ال catecholamine في المصل. رغم وجود قلة معرفة حول مقدار نشاط الجهاز الودي المتزايد بعد احتشاء العضلة القلبية الحادّ، من المحتمل ان يكون التحرّي لقيمة chromogranin A في البلازما (كمقياس كمّي لهذا الغرض) ذا أهمية سريرية. الهدف من الدراسة تقييم نشاط الجهاز العصبي الودي بعد احتشاء العضلة القلبية الحادّ بطريقة كمّية خلال قياس مستوى chromogranin A في البلازما.

طرق البحث: الاشخاص المشمولين في هذه الدراسة قسموا الى مجموعتين: خمس و اربعون مريضا من المصابين باحتشاء العضلة القلبية الحاد و ثلاثون شخصا طبيعيا. تم ملأ استمارة الاستبيان لكلا المجموعتين، ثم تم قياس تراكيز ال troponin I بجهاز VIDAS و CK–MB بطريقة Kinetic و تركيز ال chromogranin A في البلازما بطريقة ELISA. تم اخذ نماذج من مجموعة المصابين باحتشاء العضلة القلبية خلال 24 ساعة من بدء علامات المرض.

النتائج: لوحظ زيادة معنوية في معدل مستوى ال chromogranin A عند المرضى المصابين باحتشاء العضلة القلبية مقارنة مع الاشخاص الطبيعيين (307.4 P<0.001) (182.6 ng/ml Vs بالتتابع. قيمة مستوى chromogranin Aفي البلازما اكبر او يساوي 252.1 ng/ml له دقة 77.3% ، حساسية 64.4% و خصوصية 96.7% لاثبات زيادة نشاط الجهاز العصبي الودي عند المرضى المصابين باحتشاء العضلة القلبية الحاد. المرضى المصابين باحتشاء العضلة القلبية نوع inferior لم يتبين عندهم اي اختلاف مقدر في مستوى ال chromogranin A في البلازما مقارنة مع احتشاء العضلة في المواقع الاخرى من جدار القلب (306.8 ng/ml) 308.1 Vs بالتتابع. في مرضى احتشاء العضلة القلبية، تبين وجود انخفاض معنوي في نشاط الجهاز العصبي الودي (متمثلا بمستوى ال chromogranin A في البلازما) بعد استلامهم المورفين مقارنة مع المرضى الذين لم يعالجوا بالمورفين (236 Vs 325.2 ng/ml, P = 0.01) بالتتابع، بينما لم يتأثر مستوى ال chromogranin A في البلازما بالجنس و داء السكّري و التدخين.

الاستنتاجات: يمكن استخدام قياس مستويات ال chromogranin A في البلازما لتقييم درجة الزيادة في نشاط الجهاز العصبي الودي بعد احتشاء العضلة القلبية الحاد. احتشاء العضلة القلبية نوع inferior و الاحتشاء في المواقع الاخرى من جدار القلب لهما نفس درجة الزيادة في نشاط الجهاز العصبي الودي. و اخيرا المورفين يغير استجابة الجهاز الودي بعد احتشاء العضلة القلبية الحاد.

CONGENITAL HEART DISEASE IN DOWN SYNDROME: EXPERIENCE OF KURDISTAN OF IRAQ

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Submitted 2 Nov 2010; accepted 3 Dec 2011

ABSTRACT

Background and objectives Congenital cardiac disease is the commonest cause of death in patients with Down's syndrome during the first two years of life, with 40-65% of the patients having congenital cardiac malformations. The lesions can be single or multiple. Our objective was to evaluate the frequency and type of such congenital cardiac malformations in patients born with Down's in Kurdistan of Iraq.

Methods We reviewed all patients with Down's syndrome who underwent a cardiologic screening examination from January 2009 to June 2010, in the Pediatric Cardiology Department in Pediatric Teaching Hospital in Sulaimany.

Results Of the total 445 Down syndrome cases, 236 (53%) patients with Down syndrome found to have congenital heart disease, 124(52.5%) patients were male and 112(47.5%) patient were female, and among the total number 173(73.3%) patients had isolated congenital heart disease and 63(26.7%) patients presented with associated congenital heart defect. Ventricular Septal Defect was the most common single malformation, found in almost 39.3% of all cases and Atrioventricular Septal Defect found in 21.3%, Patent Ductus Artriosus account for 18.4%, and also Atrial Septal defect and Patent Ductus Artriosus was the most common associated anomalies in 25% of associated anomalies cases.

Conclusions The high frequency of ventricular septal defect, and the differential distribution of the cardiac malformations associated with Down syndrome among Kurdish children, differs from what has been reported in the United States of America, Europe, and surrounding countries in Asia, but similar results have been found in Malaysian, Chinese and Hong Kong studies. This difference warrants further research.

Duhok Med J 2011;5(2): 24-33.

Key words: Down syndrome, Ventricular septal defect, Atrioventricular septal defect, Experience

Congenital cardiac malformations continue to pose a significant problem in public health Worldwide .[1,2] Such malformations include all structural and functional cardiac defects present at birth, even if discovered later in life.[3] The incidence of such lesions is commonly reported as 8 children in each 1,000 live births.[1–3]

About half of all deaths in children with such congenital cardiac malformations occur within the first year of life. After the first year of life, however, the mortality rate for children with congenital cardiac disease is similar to that of other children without such disease.[3]

Among all patients having congenital cardiac disease, up to one tenth exhibits Down's syndrome, while between two-fifths and two-thirds of those with Down's syndrome have an associated congenital cardiac malformation.[4–11]

Trisomy 21, Down syndrome, is one of a number of chromosomal abnormalities associated with congenital heart disease. Recent studies indicate that approximately 5% of all congenital heart defects are associated with some form of chromosomal abnormality the majority of which are Down syndrome.[12-15] Endocardial cushion defect and ventricular septal defects (VSD) both have been

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reported as the most common. The association between endocardial cushion defects and Down syndrome is so striking that when an endocardial cushion defect is diagnosed in an infant, the possibility of Down syndrome always should be considered.[12, 16-18]

Down syndrome tends to be associated with the more severe forms of endocardial cushion defect.[12]

The VSD in patients who have Down syndrome has been found to be of a different type than that seen in other children. Inlet VSDs, rare in non-Down syndrome children who have ventricular defects, are common in trisomy 21.[12, 19-21]

The type of congenital cardiac disease in patients with Down's syndrome is known to vary according to geographical location. In the United States of America and Europe, an AVSD with common valvar orifice is the commonest malformation, being found in up to three-fifths of patients.[3,5,8,18,22–38]

In Asia, in contrast, a single VSD defect is reported to be the most common defect, seen in about two-fifths,[9,10] while in Latin-America, an ASD in the oval fossa was reported to be the most common lesion, again seen in about two-fifths of cases.[6]

Diagnosis is rapid, non-invasive, and definitive by echocardiography. It is best performed under the direction of pediatric cardiologists, who have the necessary equipment, technical skill, and clinical experience.[17] Pulmonary vascular disease is more common and occurs at an earlier stage in babies with Down's syndrome and congenital heart disease,[9] particularly in those with large left to right shunts.[9,10] Such babies have a higher pulmonary artery pressure both at cardiac catheterization[9] and preoperatively than have normal babies. About 30-40% of children have irreversible changes precluding surgery at the time of presentation.[10,29]

All patients who have large VSDs, with or without endocardial cushion components, are candidates for the development of pulmonary vascular obstructive disease (Eisenmenger syndrome). In the non trisomy patients, if these large defects are not corrected, pulmonary vascular disease may occur as early as 2 years of age. In patients who have Down syndrome, the problem may have its onset as early as 6 months of age.[12] Down syndrome children who have congestive heart failure and pulmonary hypertension should undergo surgical management (reparative or palliative) prior to 6 months of age to prevent the development of Eisenmenger syndrome.[12]

METHODS

We reviewed 445 cases with Down syndrome for whom we did cardiological screening examination between January 2009 to June 2010 in the Pediatric Cardiology Department / Pediatric Teaching Hospital in Sulaimany/Kurdistan /Iraq.

The unit provides pediatric cardiological assessment for over 1.5 to 2 million people (excluding those going to private clinics which are few) in Kurdistan and nearby regions. Children have been referred from general pediatricians, public hospitals and Children rehabilitation center (CRC) which deal with debilitated children, for diagnosis and treatment of their condition related to heart.

All diagnosis of Down syndrome depends on clinical criterion. Data taken for each patient include name, age,sex,type of congenital heart disease.

The types of congenital heart disease was assessed by transthoracic echocardiography with Siemens cypress machine with 2 probes 3c Mega Hertz (MH), 7cMH by 2 Dimensional and Doppler study by the same echo-cardiographer.

RESULTS

Of the total 445 Down syndrome cases, 236 (53%) patients with Down syndrome

were found to have congenital heart disease, 124 (52.5%) patients were male and 112 patient were female (Table 1), and among the total number, 173 patients had isolated CHD and 63 patients presented with associated congenital heart defect i.e. two and more defects (Table 2). Thirty-one percent of the patients were from Sulaimanya, 24% from Erbil, 23% from Duhok and 22% from Kirkuk (Figure 1).

Table 1. Sex distribution among Down syndrome cases

Sex	No. (%)
Male	124 (52.5)
Female	112(47.5)
Total	236

Table 2. Types of congenital heart disease in Down syndrome

Type	No. (%)
Single cardiac defects	173(73.3)
Associated cardiac defects	63(26.7)
Total	236

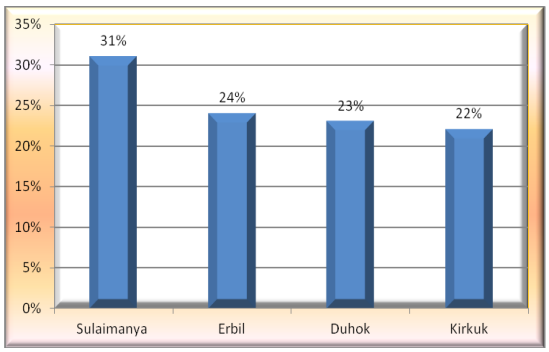

Figure 1. Distribution of Down syndrome cases according to cities of Kurdistan

Table 3 and 4 shows the types of single and also associated congenital heart disease among Down syndrome cases, in which VSD is the most common single cardiac anomaly prevalent in Kurdish people and also the ASD+ patent ductus artriosus (PDA) is the most common association anomaly in these patients.

Table 3. Types of isolated congenital heart disease in Down syndrome cases

Type	No. (%)
Complete AVSD	37 (21.3)
Partial AVSD	6 (3.4)
Intermediate AVSD	3 (1.7)
Transitional AVSD	2 (1.1)
VSD	68(39.3)
PDA	32 (18.4)
ASD	14 (8)
TOF	6 (3.4)
AS	1 (0.5)
Dilated cardiomopathy	1 (0.5)
Bicuspid aortic valve	1 (0.5)
TAPVR to SVC	1 (0.5)
PPHT	1 (0.5)
Total	173

AVSD: atrioventricular septal defect, VSD: ventricular septal defect, PDA: patent ductus artriosus, ASD: atrial septal defect, TOF: Tetrallogy of Fallot, AS: aortic stenosis, TAPVR: Total anomalus pulmonary venous return, PPHT: persistent pulmonary hypertension

Pulmonary hypertension occurs more commonly in AV cannel than in VSD cases among cases of Down syndrome with unprotected pulmonary circulation associated no pulmonary stenosis.

Figure 2 shows that pulmonary hypertension assessed by echo study is more common in cases of AVSD than VSD alone in which among 36 patients with isolated VSD 13 affected by pulmonary hypertensive disease in contrast among 40 patients with isolated AVSD, 27 patients have pulmonary vascular disease, Chi square done on the results between two kinds of defects shows statistically significant results indicating that AVSD is more likely to cause pulmonary hypertension than in case of VSD alone (P value is 0.0054).

Figure 3 shows that the subaortic type of VSD accounts for 78% of cases of VSD, the inlet type for 16% and the muscular type for 6%.

Table 4. Types of associated congenital heart disease in Down syndrome cases

Associated defect	ASD	VSD	PDA	AV cannel	Total
ASD+PDA	21	0	21	0	21
CoA with PDA	0	0	2	0	2
ASD+PS	2	0	0	0	2
AVSD+PS+PDA	0	0	2	2	2
AVSD+PDA	0	0	4	4	4
AVSD+PS	0	0	0	2	2
AVSD+ASD	4	0	0	4	4
AVSD+ASD+PDA	0	0	2	2	2
AVSD+TGA+PDA	0	0	1	1	1
AVSD+ASD	1	0	0	1	1
TOF+ASD	3	0	0	0	3
VSD +PS	0	2	0	0	2
VSD+ASD+ PDA	5	5	5	0	5
VSD+ASD	4	4	0	0	4
VSD+PS+AS	0	1	0	0	1
VSD+PDA	0	6	6	0	6
VSD+AS	0	1	0	0	1
Total	39	19	42	16	63

CoA: Coarctation of aorta, PS: pulmonary stenosis, TGA: transposition of great arteries

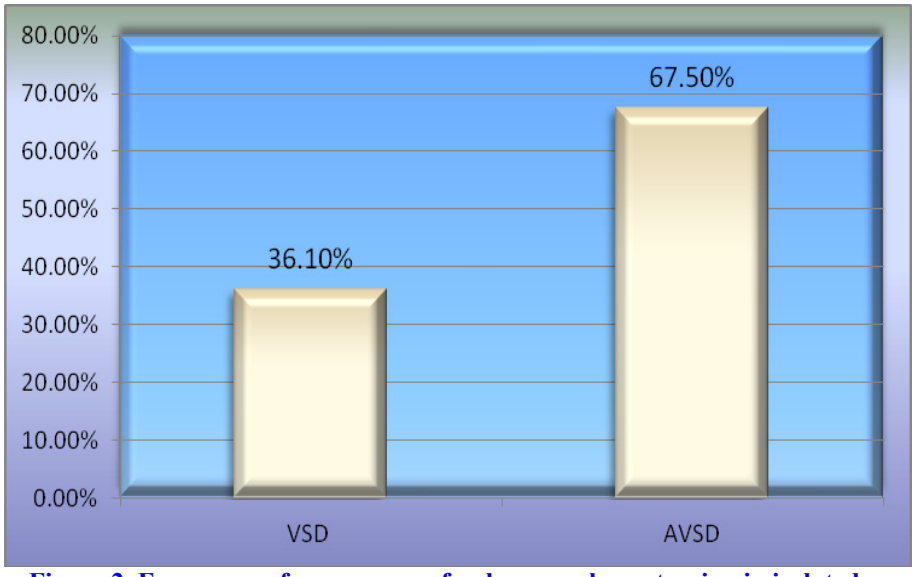

Figure 2. Frequency of occurrence of pulmonary hypertension in isolated congenital heart disease with unprotected pulmonary circulation

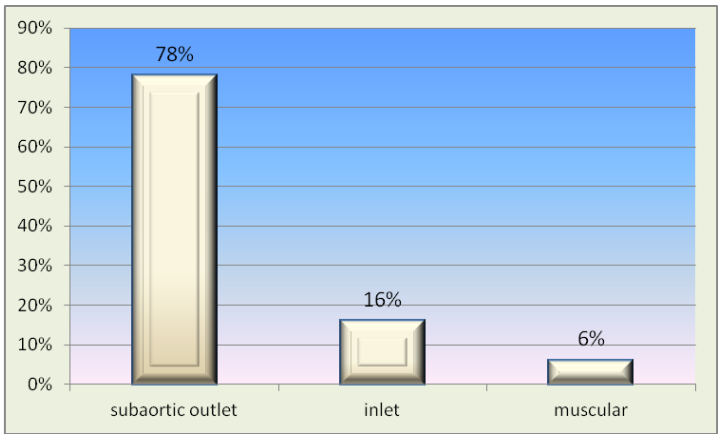

Figure 3. Frequency of types of Ventricular septal defects in cases of Down syndrome

DISCUSSION

When children are born with Down's syndrome, the presence of an associated congenital cardiac malformation is known to increase mortality in the first two years of life.[18,22]

We found that nearly half of our patients got congenital heart disease; this prevalence is similar to that recorded in United States of America, Europe and Mexico.[3-5,16,28,30,31]

In Kurdistan of Iraq, however, ventricular septal defect was the most common single malformation, found in almost 39.3% of all cases, which is similar to data from other countries, as Hongkong ,[7] Malaysia (41%),[9] China (43.6%),[10] and Danmark (49%).[24]

The second most common CHD in Kurdistan region is AVSD which account for 27.5% of all types of AVSD, where in china was 15.4%,[10] and in Denmark was 24.7%,[24] they are like this study where AV cannel is the second most common type, but in most of the studies the AVSD is the most common defect in Down syndrome; table below shows that.

Table 5. Comparison of present* and published studies on congenital heart defects in Down syndrome

Place of Study	Year	No. of DS patients	No. (%) with CHD	Commonest CHD
Kurdistan-Iraq*	**2009-2010**	**445**	**236 (53)**	**VSD**
Malaysian[9]	**1986-1987**	**34**	**17**	**VSD**
Laursen [24]	**1976**	**NR**	**80**	**VSD**
China[10]	**1989**	**NR**	**149**	**VSD**
France[32]	**1979-96**	**398**	**184(46)**	**AVSD**
Hong Kong[7]	**1994-95**	**56**	**NR**	**VSD**
Australia[33]	**1980-89**	**299**	**99(33)**	**AVSD**
Atlanta[34]	**1989-96**	**227**	**100(44)**	**AVSD**
Turkey[35]	**NR**	**31**	**20(65)**	**ASD**
Saudi Arabia[36]	**1987-96**	**37**	**13(35)**	**AVSD**
Alabama[37]	**1988-92**	**102**	**49(48)**	**AVSD**
Dallas[38]	**1993-99**	**191**	**73(38)**	**AVSD**
Chile[39]	**1990-97**	**53**	**16(30)**	**NR**
Oman[40]	**1995-98**	**90**	**54(60)**	**AVSD**

** Present study, NR mean not recorded*

In Guatemala,[11] however, patency of the arterial duct was the most common single malformation, found in almost three-tenths of patients. This differs considerably from findings in other countries, where an isolated duct is reported only to occur in about one-tenth of patients.[6,7,9,10] In Kurdistan study PDA accounted for 18.4% of all Down syndrome cases which is the third common type of congenital heart disease and its reported to be 9% in Oman,[40] but it's as high as 17.8% in Malaysian.[9]

ASD is the 4th kind of congenital heart disease in Down syndrome in Kurdistan which account for 8%, which is the third most common in Guatemala study (12.7%),[11] and also third most common in China study (13.4%),[10] and is 2nd most common in Oman study (33.3%).[40]

The distribution of associated cardiac defects in Down syndrome in which, in the Kurdistan study the ASD and PDA is the most common defects are found which account for one third of cases. In contrast in Guatemala study VSD and PDA is most common associated cardiac defect accounts for 9.6% , but ASD and PDA accounts for only 4.2%,[11] and in Malaysian VSD and PDA accounts for 11.8%,[9] and more recent study done in Dutch between 2003 to 2006 where VSD and ASD accounts for half of combine defects.[41]

The least common single and even associated defects is that of left side of the heart as aortic stenosis, coarctation of aorta and transposition of great arteries which account in Kurdistan study between 0.5-1.5% of Down syndrome cases with cardiac defect; the same results found in European and Asian studies.[40,41]

As far as we are aware, this study is the first epidemiologic study concerning the frequency and types of congenital cardiac disease in Kurdistan children with Down syndrome.

In conclusion this hospital based study of children with Down syndrome showed relatively high frequency of congenital heart disease, the commonest being VSD in which the subaortic type is the commonest subtype. Atrioventricular cannel is the 2nd most common type which is recorded in most parts of Europe and USA to be the commonest type, but not in Asian countries, so ethnicity may have role in this distribution, and need further investigation. Left side anomalies were least common type of defects, as coarctation and aortic stenosis.

ACKNOWLEDGMENTS

I would like to express my profound gratitude to all my colleagues who helped me and referred patients form different areas in Kurdistan. Great thanks to my family for support, especially my wife.

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پوختە

نەخۆشیە زگماکەکانی دڵ لەو منداڵانەی کە نەخۆشی مەنگۆلیان هەیە – کوردستانا عیراقێ

پێشەکی و ئارمانج: نەخۆشیە زگماکەکانی دڵ هۆکاری زۆری مردنەکانن لەو منداڵانەی کە نەخۆشی مەنگۆلیان هەیە لە ماوەی دوو ساڵی یەکەمی تەمەندا کە بە ڕێژەی 40–60٪ ی ئەم نەخۆشانە کێشەیەکی دڵیان هەیە کە بە تەنیایە یان جۆراو جۆرە. ئامانجمان لەم لێکۆڵینەوەئەوەیە کە هەڵسەنگاندنێك بۆ جۆری کێشە زگماکییەکانی دڵ بکەین لە جۆری مەنگۆل لە کوردستانی عێراق.

ریکێن ڤەکولینێ: هەموو ئەو نەخۆشیە مەنگۆلیانە وەرگیراون و پشکنینیان بۆ کراوە لە ماوەی نێوان مانگی کانونی دووەمی 2009 بۆ مانگی حوزەیرانی 2010 لە بەشی دڵی منالاڵن سەر بە نەخۆشخانەی منالاڵنی فێرکاری لە سلێمانی.

ئەنجام: (445) نەخۆشی مەنگۆل(236) نەخۆشیان کێشەی زگماکی دڵی هەبووە . کە (124) منالّ (52,5٪) نەخۆشیان کوڕن وە (47,5٪) کچ بوون. وە لە ژمارەی گشتییەکە (173) منالّ (73,3٪) نەخۆشەکان تەنها یەك جۆر یان هەبوو. وە (63) منالّ (26,7٪) چەند جۆریکیان هەبووە لە یەك نەخشدا کە جۆری کونی دڵ لە نێوان هەردوو سکۆڵەدا زۆرترینیان بوو کە ڕێژەی (39,3٪) بوو کە بە ڕێژەی یەکەم هاتووە. جۆری کونی دڵ لە نێوان سکۆڵەکان و گوێچکەلەکان بە ڕێژەی دووەم دێت کە ڕێژەکەی (18,4%٪) جۆری کونی دڵ لە نێوان گوێچکەلەکان لەگەڵ بۆری دەرەوەی دڵ (PDA) لە هەمان نەخۆشدا ڕێژەکەی گەشتە (25٪) ی ئەو نەخۆشانەی لە یەك زگماکی زیاتریان هەیە.

دەرئەنجام: ڕێژەی کونی زگماکی دڵ لە نێوان سکۆڵەکان لە نەخۆشی مەنگۆل کوردستان دا بە ڕێژەی یەکەم دێت کە جیاوازە لەوەی لە ئەمریکا و دەوڵەتەکانی دەوروبەرمان و کەنداو بەڵام هەمان دەرەنجام هەیە لە چین و مالیزیا و هونج کونج ئەم جیاوازیە پێویستی بە لێکۆڵینەوە ی زیاترە.

الخلاصة

أمراض القلب الخلقية في متلازمة داون: كردستان العراق

خلفية واهداف البحث: أمراض القلب الخلقية هي السبب الأكثر شيوعا للوفاة في المرضى الذين يعانون من متلازمة داون المنغولية خلال فترة أول عامين من العمر، مع 40–65 ٪ من المرضى الذين يعانون من تشوهات القلب الخلقية. يمكن أن تكون الآفات مفردة أو متعددة. كان هدفنا من أجل تقييم وتيرة ونوع تشوهات الخلقية تلك أمراض القلب في المرضى الذين يعانون يولدون مع داون في كردستان العراق.

طرق البحث: قمنا بمراجعة جميع المرضى الذين يعانون من متلازمة داون الذي خضع لفحص الكشف cardiologic من يناير2009 الى يونيو 2010، بقسم أمراض القلب للأطفال بالمستشفى الأطفال التعليمي في السليمانية.

النتائج: من مجموع 445 حالات متلازمة داون، وجدت 236 مريضا المصابين بمتلازمة داون أن يكون أمراض القلبالخلقية، 124 (52.5%) من المرضى من الذكور و 112 (47.5%) من المرضى من الإناث، وبين العدد الاجمالي قد 173 (73.3 ٪) من المرضى بأمراض القلب الخلقية معزولة و 63 (26.7 ٪) من المرضى قدم المرتبطة مع عيب خلقي في القلب. كانت العيب في الحاجز البطيني تشوه الأكثر شيوعا واحد، وجدت في ما يقرب من 39.3 ٪ من جميع الحالات. عيب الحاجز الأذيني البطيني وجدت في 21.3 ٪، الواسلة الورمدين وجدت في 18.4% ، وعيب الحاجز الأذيني و الواسلة الورمدين كان التشوهات الاكثر شيوعا المقترنة في 25 ٪ من الحالات التشوهات المرتبطة بها.

الاستنتاجات: وتيرة عالية من عيب الحاجز البطيني، وتوزيع الفرق في التشوهات القلبية المرتبطة متلازمة داونبين الأطفال الأكراد، يختلف عن ما تم الإبلاغ عنها في الولايات المتحدة الأمريكية، وأوروبا، والبلدان المحيطة بها في آسيا، ولكن النتائج نفسها وجدت في صينية وماليزية ودراسات هونغ كونغ. هذا الاختلاف يبرر إجراء مزيد من البحوث.

MODIFIED ONE STAGE MUSTARDEE HYPOSPADIAS REPAIR: A REVIEW OF 55 PATIENTS

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Submitted 11 Dec 2010; accepted 3 Dec 2011

ABSTRACT

Background and objectives Hypospadias is a common congenital anomaly. Many methods for repair of hypospadias have been emerged; all have the same objective. Recently several surgeons recommended one-stage hypospadias repair. The objective of the study was to determine the operative time and outcome of hypospadias repair by one stage tabularized ventral penile skin flap urethroplasty.

Methods This study was a review of 55 patients who had been diagnosed with hypospadias. The study was conducted at Azadi General Teaching Hospital in Duhok governorate, Kurdistan region, Iraq between June 2006 and February 2007. This is the main referral hospital in Duhok where patients with urologic problems receive medical care. All patients underwent a one stage hypospadias repair using premeatal based tube flap repair (a modified Mustardee operation).

Results A total of 55 patients included in the study with a median age of patient of 4 years (range 9 months – 30 years). The operative time was 60 minutes with a range of 50-70 minutes. Complications were occurred in about half of the patients but most subsided with further conservative or surgical intervention. Fistula formation was the commonest one (21.8%) followed by meatal stenosis (12.8).

Conclusions Final outcome following modified Mustardee operation is comparable to the other techniques and surgeons can be encouraged to perform such technique.

Duhok Med J 2011;5(2): 34-41.

Key words: Hypospadias, One stage repair, Urethroplasty, Duhok

Hypospadias is a congenital abnormality of the penis which results in an incomplete development of the anterior urethra. It is characterized by malpositioning of the opening of the urinary meatus on the ventral aspect of the penis proximal to the tip of the glans penis. The urethral opening may be anywhere along the shaft of the penis, within the scrotum or even in the perineum. Chordee, which is ventral shortening and curvature, is often associated and usually with more proximal urethral defects.[1-3]

The prevalence of hypospadias varies widely across different population and is estimated to be between 1 in 300 and 1 in 250 male births.[4,5] Rate of hypospadias had doubled between 1970s and 1990s in the United States and several European countries.[6,7]

It is recognized that the etiology of hypospadias is multifactorial comprising hereditary, genetic, endocrinal and environmental.[1,8,9]

Hypospadias is classified based on the location of abnormal urethral meatus. Although several different classifications have been suggested; however, many physicians have adopted the classification that was proposed by Barcat.

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This classification is based on the location of the meatus after correction of associated chordee.[3] This classification includes three principle types: anterior (glandular, coronal or distal), middle, and posterior (posterior penile, penoscrotal, scrotal, or perineal).[1,10]

The field of hypospadias remains full of challenges in the search for the new and better solutions. Many types of surgical procedures have developed all of which have principle objectives, with optimum results and less complications, of improving the functional aspects of penis, permitting urination standing up.[3] So surgery is technically demanding but the results may be less than satisfactory.[11] Complications includes fistula formation, meatal stenosis, stricture and disruption.[3,12] Cosmetic outcome is important specially nowadays in some centers.[13]

The objectives of this study were to determine the operative time and outcome of hypospadias repair by one stage tabularized ventral penile skin flap urethroplasty.

METHODS

This study was a review of 55 patients who had hypospadias. The study was conducted at Azadi General Teaching Hospital in Duhok governorate, Kurdistan region, Iraq between June 2006 and February 2007. This hospital is the main referral hospital for urology patients in Duhok. All patients who had hypospadias and referred to the hospital during the study period were enrolled in the study. The inclusion criteria were patient who had penile hypospadias regardless of the age and who had no or one previous surgical repair of hypospadias. A written consent was obtained from patients' parents to undergo the operation for their children. All patients were managed by the same surgical team, including the authors.

Technique

All patients underwent a one stage hypospadias repair using premeatal based tube flap repair (a modified Mustardee operation). The operation was done under general anesthesia. No tourniquet was used during the surgery.

All adhesions between glans and prepuce were removed. Meatal dilatation was done for all cases using artery-forceps with use of lidocaine gel.

Pre-meatal ventral penile skin was marked for distance equal to the distance between the meatal opening and the tip of the penis (Figure 1). Then, the skin flap was released upward till the meatal opening (Figure 2).

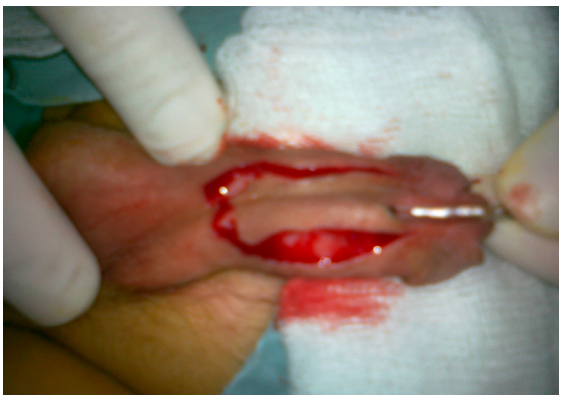

Figure1. Marking and incision of pre-meatal penile skin

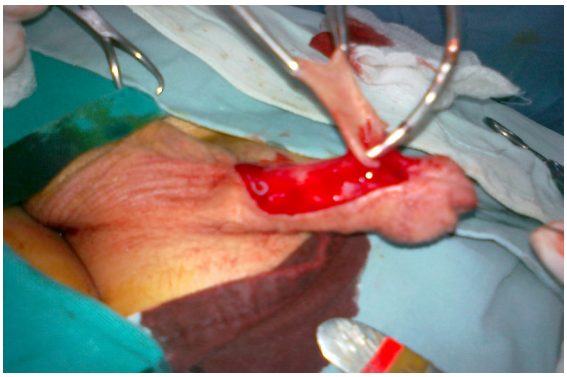

Figure 2. Releasing of the skin flap

Small horizontal incision of 1-2 cm was made in the ventral part of the skin just distal to the meatal opening and all the fibrous tissues were excised from the corpora to correct chordee. Vertical incision was done from the meatal opening to the tip of glans, bisecting the glans into two wings.

A stent was put to divert urine. For children, nasogastric (NG) tube 8 Fr was used as a catheter while in adults, Foleys catheter 12 Fr was used.

A tube was made from the skin flap around the NG tube and stitched intermittently using 6/0 PDS suture with the suture line located posteriorly (Figure 3).

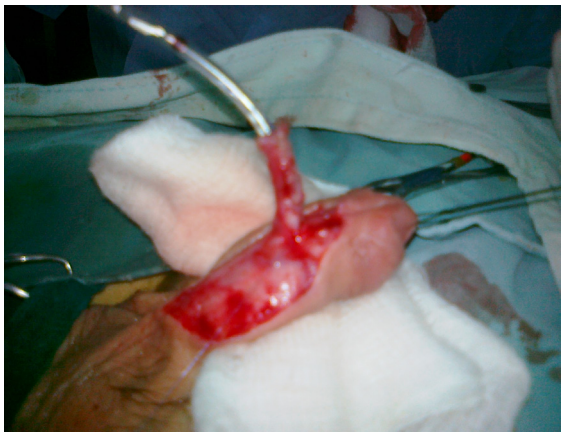

Figure 3. Tube formation from the skin flap around the nasogastric tube

The end of the tube was sutured to tip of the glans using 6/0 PDS sutures. Anastomosis of both wings of the bisected glans were performed anterior to the urethral tube with 2-3 interrupted stitches using 5-6/0 PDS sutures (Figure 4).

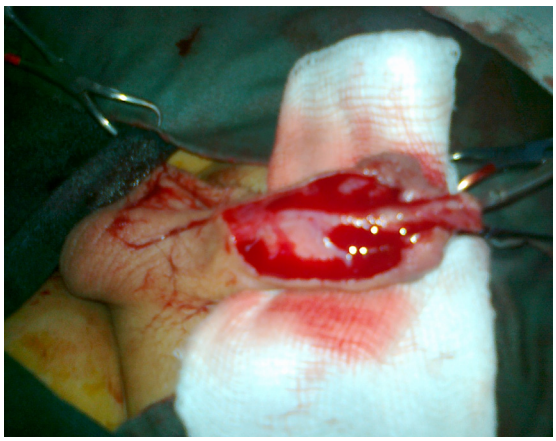

Figure 4. Suturing of the wings around the tube

For uncircumcised patients, the prepusal skin was released from the dorsum of the penis completely, divided in the middle, and then both parts of the prepuce were brought anteriorly and sutured ventrally to cover the raw area using 6/0 PDS sutures (Figure 5). For circumcised patients, the raw area was covered by rotational skin flap from the base of penis or sides of scrotum.

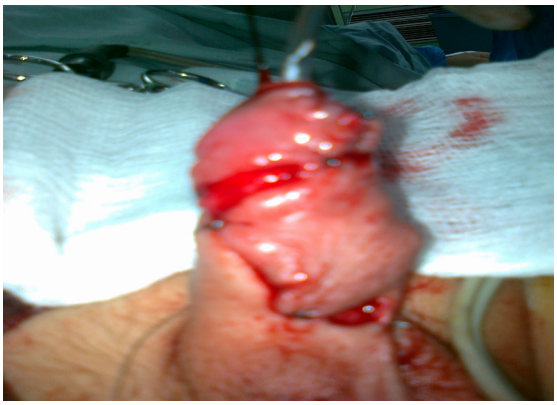

Figure 5. Release of prepusal skin and anterior suturing

Hemostasis was done by direct pressure and bipolar cautery.

NG tube was fixed to the tip of the glans using 3/0 silk stay suture. The tube was connected to a closed drainage system, and fixed by plaster to the abdomen (Figure 6).

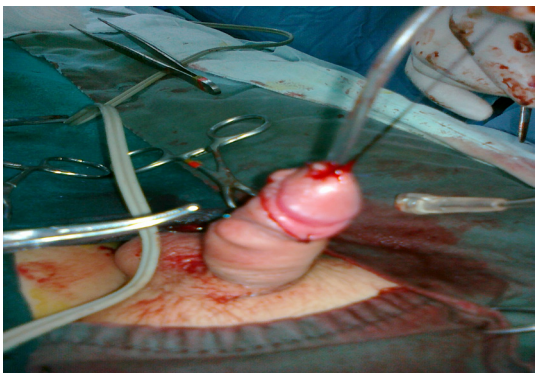

Figure 6. The end results of Mustardee technique

Loose dressing was done using sofratol and gauze plaster. Dressing was changed on the 5th postoperative day and thereafter on every other day.

All patients were given antibiotics prophylactic (cefotaxime). Antispasmodics and analgesics were used and high fluid intake was encouraged to avoid blockage

of the catheter. Sometimes, irrigation through the catheter was done to avoid any blockage. Adults patients were given estrogen to avoid erection.

All patients were kept in the hospital for 10 days. Catheter was left in for 10 days. Patients were discharged on 11th post operative day after urine per urethra was passed and urine stream was observed. Patients were followed up during admission, at 2 weeks, at 1month and at 3 months.

RESULTS

Fifty-five patients with hypospadias presented to the Urology department in Azadi General Teaching Hospital during the study period were included in the study and operated on. All patients were followed up for a minimum of 3 months and for 6 months in most patients. The time required to perform the operation was 50-70 minutes with a median of 60 minutes.

Patients ranged in age from 9 months to 30 years (median 4 years). Forty-two patients (76.4%) were brought by their parents and 13 cases (23.6%) were referred by either pediatrician or by self-seeking.

Forty-seven patients (85.5%) had chordee at the time of operation with different degrees of severity. Only 19 patients (34.5%) were circumcised at the time presentation. History of previous hypospadias repair was encountered in 13 patients (23.6%).

Table 1 shows distribution of patients according to the types of hypospadias. Around half of the patients had middle followed by distal penile hypospadias, 28 patients (50.9%) and 21 patients (38.2%), respectively.

Table 1. Distribution of patients according to the types of hypospadias (N = 55)

Type	No. (%)
Distal penile	21 (38.2)
Middle penile	28 (50.9)
Proximal penile	5 (8.9)
Peno-scrotal	1 (1.8)

Thirty-two patients (58.2%) developed no complication at all during their whole follow up period while one or more complications, whether minor or major, were encountered in the rest. Major complications, one or more, were encountered in 21 patients (38.2%). Table 2 illustrates complications developed by patients at different postoperative times. Fistula was seen in 12 patients (21.8%). In 4 patients, fistula was repaired by surgery and in other 2 patients, surgery was planned for. In three patients, catheter placed in again and the fistula healed later on. Fistula in the rest healed spontaneously after patients treated for other associated complications. Meatal stenosis was noticed in 10 patients (18.2%) in whom subsequent regular meatal dilatation was performed. Chordee seen in one patient for whom further surgical intervention was planned to correct for the chordee. Reccurence of the hypospadias was observed in only one case during the follow up period.

Table 2. Complications developed by patients at different postoperative times

Complication	No. (%)
Minor complications	
Wound infections	9 (16.4)
Obstructed catheter	2 (3.6)
Major complications	
Fistula	12 (21.8)
Meatal Stenosis	10 (18.2)
Chordee	1 (1.8)
Disruption (recurrence)	1 (1.8)

DISCUSSION

Hypospadias is a common clinical problem.[10] Many methods of operations have been introduced to repair hypospadias. The goal of repair is functionally and cosmetically normal penis. Many surgeons prefers two-stage procedure[14] while other recommends one-stage procedures.[15-17] This implies that there is no standard technique.

Authors of this study adopted a

modification of Mustardee method of repairing hypospadias, which depend on the construction of new urethra from the premeatal skin. In additions, the authors separated the glans by vertical incision in the glanular groove forming two wings to cover the tabularized-urethra in 2 layers.

Around half of patients developed complications. The reported incidence of complications range from 6 to 30%, varying with the severity of the hypospadias.[18,19] This noted discrepancy between this study and the reported incidence in the literature might be because several factors are included in the development of complications, for example age. The median age of patients at operation in this study was 4 years while the optimum age for correcting hypospadias infancy.[20,21]

The rate of fistula was 21.8% which is comparable with that from other techniques (0-23%).[22,23] Careful preservation of vasculature of the flap and avoidance of overlapping suture lines produce a watertight closure with minimum risk of post-operative fistula formation.

The cause of chordee is tethering of hypoplastic/aplastic corpus spongiosum tissue or urethral plate with the underlying corpora. Mobilizing urethra relieves chordee in most of instances and no further procedure is required for correction of chordee.

No tourniquet was used in this method. This allowed hemostasis during operation and therefore reduced post-operative edema and hematoma . Bipolar cautery for meticulous hemostasis, direct pressure intraoperativly and loose dressing was used. Use of non-compressive dressing reduces post-operative pain and change of dressing is less uncomfortable. Authors did not attempt to measure pain objectively, but none of patients in this study needs sedation to change the first dressing. Compressing dressing is liked and used by many surgeons. but this study found that loose dressing, if there is good hemostasis, has better out come.

Hypospadias is a common disease. Patients present at different ages for repair, seeks different opinion of different surgeons for repair. Lack of preputial skin, by circumcision due to religious rules, made the repair sometimes difficult. Fistula rate among patients with hypospadias is acceptable with observance of a high percentage of fistula-repair. Final outcome was very good with s high success rate after about 3-6 months of regular follow up. In patients with previous surgery or lack of skin (circumcision), the cosmetic appearance was not as good as in patients not exposed to previous surgery or circumcision; regarding urethroplasty, the result was very good.

Modified Mustardee operation is advised for cases of proximal and middle penile hypospadias with no or mild chordee and better if they have no previous attempt for repair of uncircumcised patients. It is better to follow patients for a duration longer than 3-6 months before deciding the final outcome.

Parents are advised not to circumcise their children when there is ambiguous genitalia.

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پوختە

نشتە رکە ریا جیکرنا میزتنا ز بنفھ ب ریکا ماستاردی یا معھ دەل ب ئیك جار:دیتنا 56 نە خوشا

پێشەکی و ئارمانج: پێشەکی:میزتنا ژبنڤە ئێکە ژ نەدروستیێن زکماکی یێن مشە،و گەلەك ریێك یێن ھاتینە دیارکرن بو چێکرنا ڤێ نەدروستیێ. گەلەك نشتەرکار ل ڤێ دوماھیێ ھاندانا ریکا ئیك قوناغ دکەن بو چێکرنا نەدروستیا میزتنا ژبنڤە. ئارمانج ژ ڤەکولینێ دەستنیشانکرنا دەمێ پێدڤی و ئەنجامێن داویێ یێن نشتەرگەریا ئیك قوناغ بو چێکرنێ (one stage tabularized ventral penile skin flap urethroplasty).

ریکێن ڤەکولینێ: ئەڤ ڤەکولینە پێداچونەك بوو لسەر 55 نەخوشێن ھاتینە دەستنیشانکرن ب نەدروستیا میزتنا ژبنڤە. ڤەکولین ھاتە کرن ل نەخوشخانا ئازادی لپاریزگەھا دھوکێ– ھەرێما کوردستانێ– عیراق ھەر ژ خزیرانا 2006ێ ھەتا شواتا 2007ێ. ئەڤ نەخوشخانە یا ئێکانەیە لپاریزگەھا دھوکێ بو وەرگرتنا نەخوشێن ئاریشێن جوبارێن میزێ ھەی. بو ھەمی نەخوشان نشتەرگەریا پێدڤی یا ئیك قوناغ ھاتە کرن بریکا (a modified Mustardee operation premeatal based tube flap repair.

ئەنجام: تێکرایێ ژیێ ھەر 55 نەخوشان 4 سال بوون (9 ھەیڤ – 30 سال) و تێکرایێ دەمێ نشتەرگەریێ 60 خولەك بوون ب ریژا 50 – 70 خولەك. ئالوزییێن نشتەرگەریێ بو نێزیکی 50٪ ژنەخوشان دیاربوون بەلێ پرانیا وان ھاتنە چارەسەرکرن یان ب چاڤدێری یان ژی ب نشتەرگەری. مشەترین ئالوزی ناسور بوو (21.8٪) و لدویفدا تەنگبوونا بوریکێ (12.8٪).

دەرئەنجام: ئەنجامێ دوماھیکێ پشتی نشتەرگەریا modified Mustardee operation دیاربوو کو وەکی ریکێن دی یە و باشە نشتەرکار بھێنە ھاندان بو بکارئینانا ڤێ ریکێ.

الخلاصة

ترميم المبال التحتاني بطريقة ماستاردي المعدلة بمرحلة واحدة:مراجعة ل 56 حالة

خلفية واهداف البحث: المبال التحتاني هو شذوذ خلقي شائع. وقد ظهرت العديد من الطرق لترميم المبال تحتاني. وقد اوصى عدد من جراحي المسالك البولية مؤخرا طريقة الترميم ذات المرحلة الواحدة. الهدف هو لتحديد الزمن المطلوب والنتيجة النهائية لعملية الترميم ذات المرحلة الواحدة urethroplasy repair by one stage tabularized ventral penile skin flap.

طرق البحث: هذه الدراسة كانت استعراضا ل 55 مريض تم تشخيصهم بالمبال التحتاني. وقد أجريت هذه الدراسة في مستشفى أزادي التعليمي العام في محافظة دهوك، اقليم كردستان العراق في الفترة ما بين يونيو 2006 وفبراير 2007. وتعتبر المستشفى الوحيدة في محافظة دهوك لاستقبال المرضى المصابين بامراض المسالك البولية. و قد تم اجراء العملية اللازمة لجميع المرضى باستخدام premeatal based tube flap repair (a modified Mustardee operation).

النتائج: ما مجموعه 55 مريضا شملتهم الدراسة مع متوسط عمر المريض 4 سنوات (9 شهور -- 30 سنة). كان الزمن المستغرق لاجراء العملية هو 60 دقيقة بمعدل 50–70 دقيقة. وقد حدثت مضاعفات لعدد من المرضي ما يقارب 50% ولكن معظمهم عولجوا أما تحفظيا او بتدخل جراحي. وكان حدوث الناسور الاكثر شيوعا (21.8 ٪)، يليه تضيق الصماخ (12.8%).

الاستنتاجات: النتيجة النهائية بعد عملية modified Mustardee operation مشابه للتقنيات الأخرى، ويمكن تشجيع الجراحين للقيام بهذه التقنية.

GROWTH HORMONE AFFECTS HAIR GROWTH AND ALTERS CYCLIC HAIR CHANGES IN ALBINO MICE: A HISTOLOGICAL STUDY

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Submitted 17 Apr 2011; accepted 3 Dec 2011

ABSTRACT

Background and objectives Hair growth and development undergo cyclic changes which involve rapid remodeling of both epithelial and dermal components. Intercellular signaling molecules play an important role in this process. Growth hormone may have an essential role in hair follicle morphogenesis. This study was designed to examine the effects of growth hormone on hair follicle growth and cycling in male albino mice.

Methods Growth hormone was administered subcutaneously to 10 albino male mice at a single daily dose of 5 mg/kg for 4 weeks and its effects on hair growth were examined by measuring hair length and hair follicle histology in a pre-depilated skin patch. Plucked hair length, hair follicle stage and depth and hair bulb diameter were determined and compared with 10 control animals.

Results Treated animals showed increased plucked hair length and increased percentage of hair follicles in anagen phase with greater depth and bulb diameter. The control animals had greater percentage of catagen follicles.

Conclusions Growth hormone plays an important role in the development and maintenance of hair follicles. It can affect the hair cycle and may have antiapoptotic effects that prolong proliferative anagen phase and delay the regressive catagen pahse.

Duhok Med J 2011;5(2): 42-50.

Key words: Growth hormone, Hair cycle, Hair follicles, Anagen, Categen, Telogen

Growth hormone (GH) is a polypeptide that exerts wide metabolic effects. It directly stimulates cellular growth via growth hormone receptor (GHR), or indirectly by stimulating the expression of insulin-like growth factor-1 (IGF-1) gene via GHR in a wide range of cells such as hepatocytes, fibroblasts, keratinocytes, chondrocytes, osteoblasts and adipocytes.[1] Then IGF-1 acts on target cells by an endocrine, paracrine or autocrine fashion.[2] Studies have shown that GHRs, growth hormone-binding protein (GHBP) and IGF-1 receptors are recognized in epidermis, epidermal appendages and dermal components.[3] The formation of hair follicles occurs during embryogenesis and relies on a series of signals sent between dermal cells and overlying surface epithelial cells that cause changes in the fate of both cell populations, ultimately resulting in differentiation of the hair shaft, root sheaths, and dermal papillae.[4] A fully mature hair consists of the hair shaft (the visible portion above the surface of the epidermis) and the hair root (the portion within the hair follicle in the dermis). The hair follicle is the source of the growing hair shaft. It consists of epithelial cells (the inner and outer root sheaths) surrounded by mesodermal connective tissue (dermal) components (connective tissue sheath and dermal papilla).[5] The dermal papilla has major regulating role in hair growth and cyclic changes.[6] The hair follicle undergoes a life-long cyclic transformation from a resting (telogen) phase to a growth (anagen) phase with rapid proliferation of follicular keratinocytes and elongation and thickening of the hair shaft, followed by a regression (catagen) phase leading to

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involution of the hair follicle. These cyclic changes involve rapid remodeling of both epithelial and dermal components.[7] Intercellular signaling molecules between cells of the dermal papilla and the spinous cells of the outer root sheath play key roles in hair follicle cyclic changes.[8] This study was designed to explore the effects of GH on a regenerative epidermal derivative with stem cell component, the hair follicle.

METHODS

The experiment was designed and performed at the research laboratory of the department of anatomy in Al-Mustansiriya College of Medicine in Baghdad. Twenty male albino mice aged 16-18 weeks were used and were divided into two groups (10 each): treated and control. All animals were kept in the animal house with constant controllable temperature and a 12-12 light/dark hour schedule with free access to control diet and water.

A windowed adhesive patch (2cm X 2cm window) was used to mark a fixed area on the right side of the mid-dorsal region of all animals. The hairs were clipped from that area and Nair® depilating cream (calcium thioglycolate as active ingredient) was used to clear the area of hair and initiate anagen. The area was marked by a surgical marker pen for future reference. The treated animals received single daily subcutaneous injections of GH (Biosynthetic Nordotropin® of Novo Nordisk, Denmark) at the thigh area in a dose of 5 mg/kg for 4 weeks. The control animals received single daily subcutaneous injections of 0.9% normal saline for the same period of time.

Before the animals were sacrificed under anesthesia at the end of the 4 weeks period, 20 hairs were tweeze-plucked from the depilated patch of each animal and examined for the presence of the follicle before their lengths were measured under a magnifying glass using a steel ruler.

The depilated area of skin was then cut and the tissue was prepared for standard paraffin sections which were stained with H&E and examined under light microscopy.

The hair follicle histology was used to determine the hair stage in randomly selected 50 follicles from 5 sections for each animal and the percentage of each stage was calculated. The criteria used for distinguishing different hair follicle stages were adapted from Rover et al[5] and included hair follicle length and depth, the size and shape of the dermal papilla; hair bulb and hair club.

The thickness of hair follicles was measured at the level of the largest diameter (Auber's line) of hair bulbs with clearly visible dermal papillae using an objective micrometer eyepiece. The depth of each examined follicle from the dermal papilla to the epidermis was also recorded.

Statistical analyses were performed using SPSS Software. The results were then tabulated and statistical significance was inferred at $P<0.05$.

RESULTS

The hairs plucked at the end of the experiment were longer in treated animals as shown in table 1.

Table 1. The length of plucked hair (mm) in albino male mice treated with GH and their corresponding controls (Data represent Mean±Standard deviation)

Animal group	Plucked hair length (mm)
Treated	8.4±1.6
Control	5.2±0.9
P-value	<0.05

Microscopical examination revealed that most hair follicles were in anagen phase in all animals. The percentage of anagen follicles was significantly greater in the treated animals. Control animals had significantly greater numbers of catgen follicles. Telogen follicles were the least seen follicles in both animal groups and showed no significant difference between

the treated and control animals (Figure 1).

Anagen follicles were characterized by increasing length and depth, lying in the deep dermis and extending into the subcutis at later stages of anagen. The hair bulb is large and ball-like in dermal regions in early stages but becomes narrow and elongated closer to the subcutis in later anagen (Figure 2). The hair bulb reaches its maximum size as it resides in the subcutis just superficial to the panniculus carnosus. The inner and outer root sheaths and the elongated roots are well defined (Figure 3).

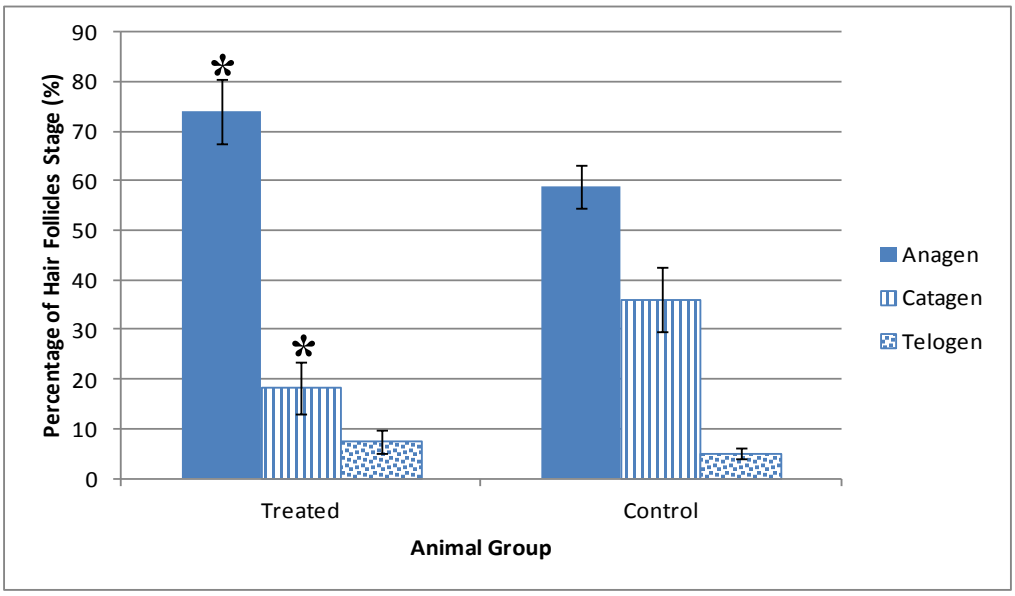

Figure 1. The percentages (%) of different stages of hair follicle growth in mice treated with growth hormone and their corresponding controls (Data represent Mean, Vertical bars represent Standard Deviation, * = significant difference)

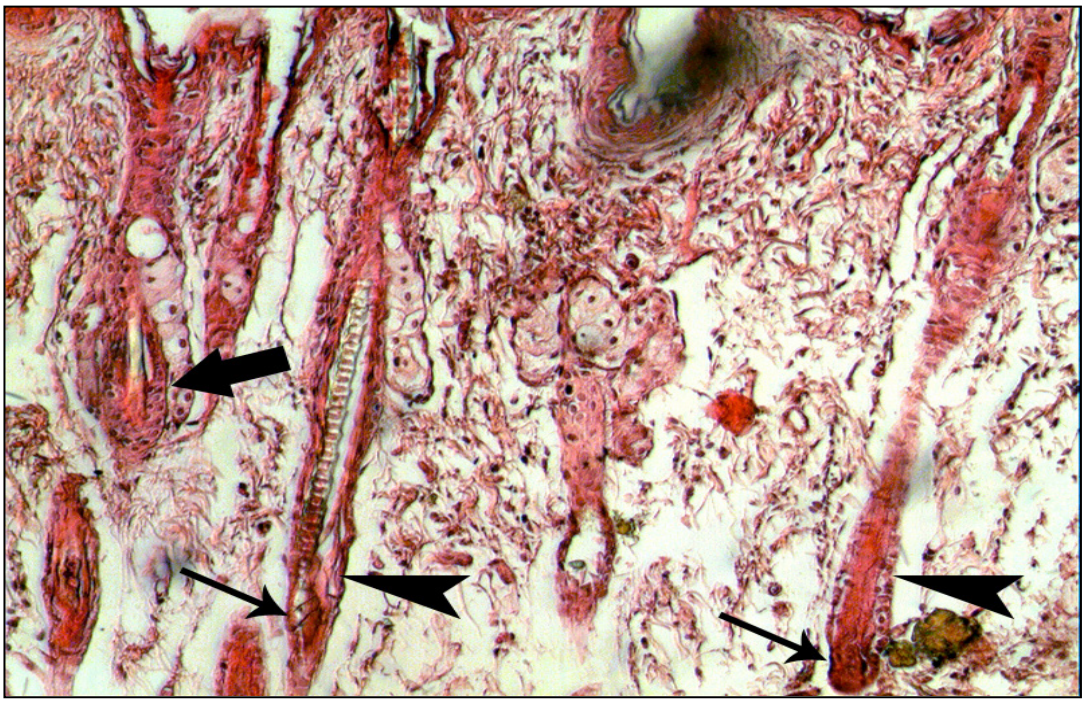

Figure 2. The skin of mice treated with GH, showing an early anagen hair follicle (thick arrow) with ball-like hair bulb and two longer late anagen follicles (arrow heads) with more elongated bulbs (narrow arrows). H&E X200

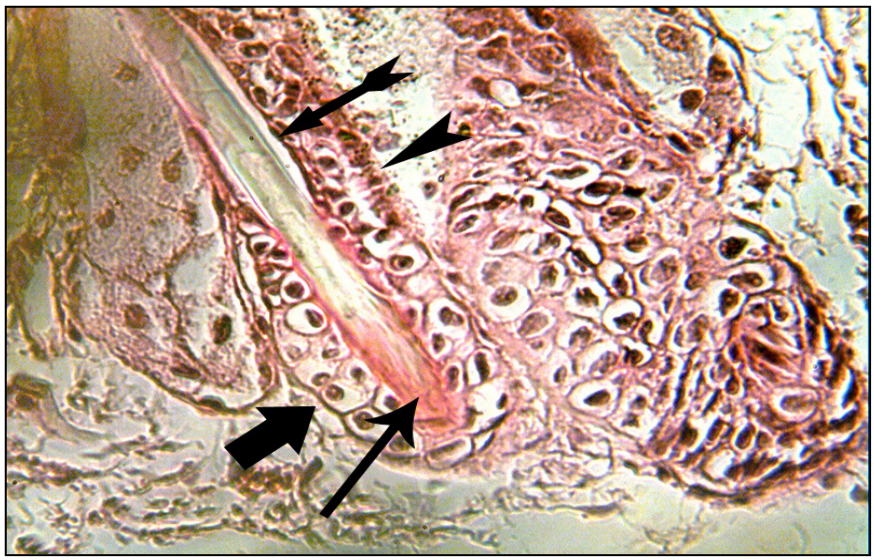

Figure 3. The skin of mice treated with GH, showing he large hair bulb of late anagen (thick arrow) with an elongated root (narrow arrow) and well defined inner root sheath (tailed arrow) and outer root sheath (arrow head). H&E X800

In catagen stages, the hair follicle is short and more superficially situated in the dermis. The dermal papilla is condensed and onion-shaped and attaches to the distant hair bulb by an epithelial streak which contains many apoptotic cells (Figure 4). In later catagen, the streak disappears and the hair bulb seals off into a rounded hair club (Figure 5).

During telogen phase, the follicles have minimal length and are most superficial in their dermal position. The dermal papilla is compact, ball-shaped and is attached to the hair club by a bag like structure of germ cells (secondary germ capsule). The hair shaft is markedly thin (Figure 6).

Hair follicles were significantly more deeply seated in treated animals than in controls. The hair bulb diameters were also greater (Table 2).

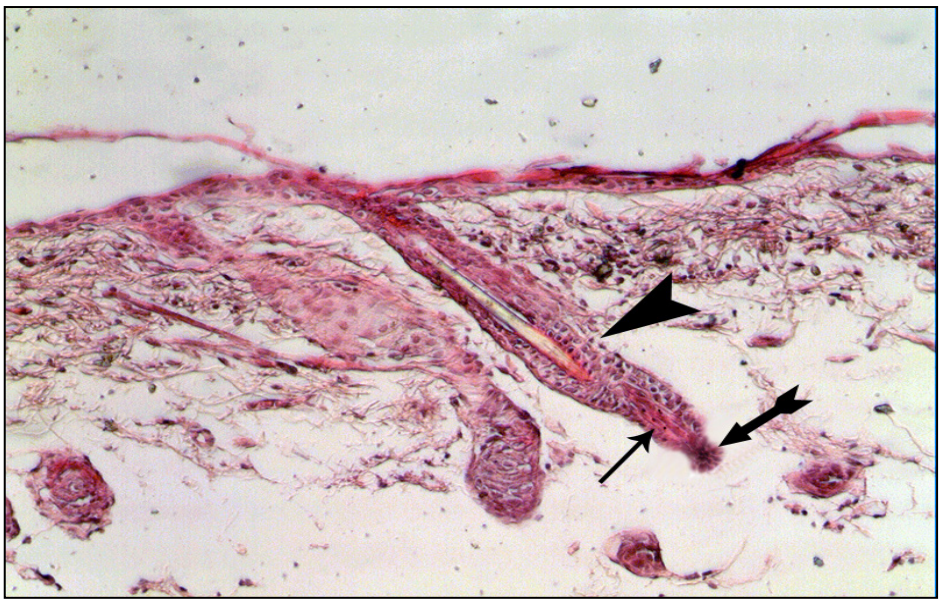

Figure 4. The skin of control mice, showing early catagen hair follicle (arrow head) with a superficial position in the dermis, condensed onion-shaped dermal papilla (tailed arrow) and an epithelial streak (narrow arrow) attaching the papilla to the hair bulb. H&E X200

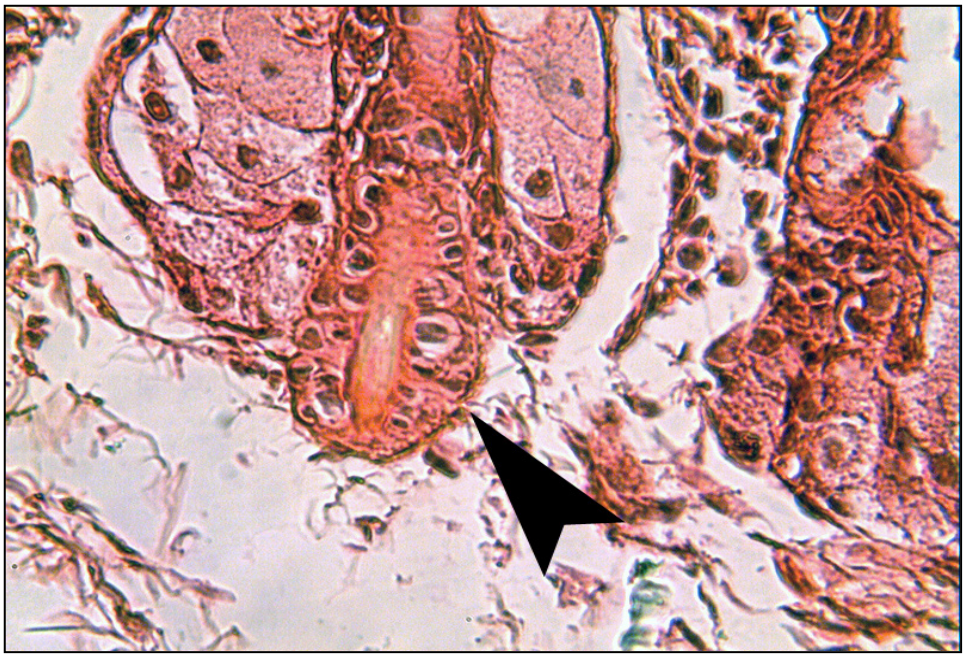

Figure 5. The skin of control mice, showing a club hair bulb (arrow head) of late catagen hair follicle. H&E X800

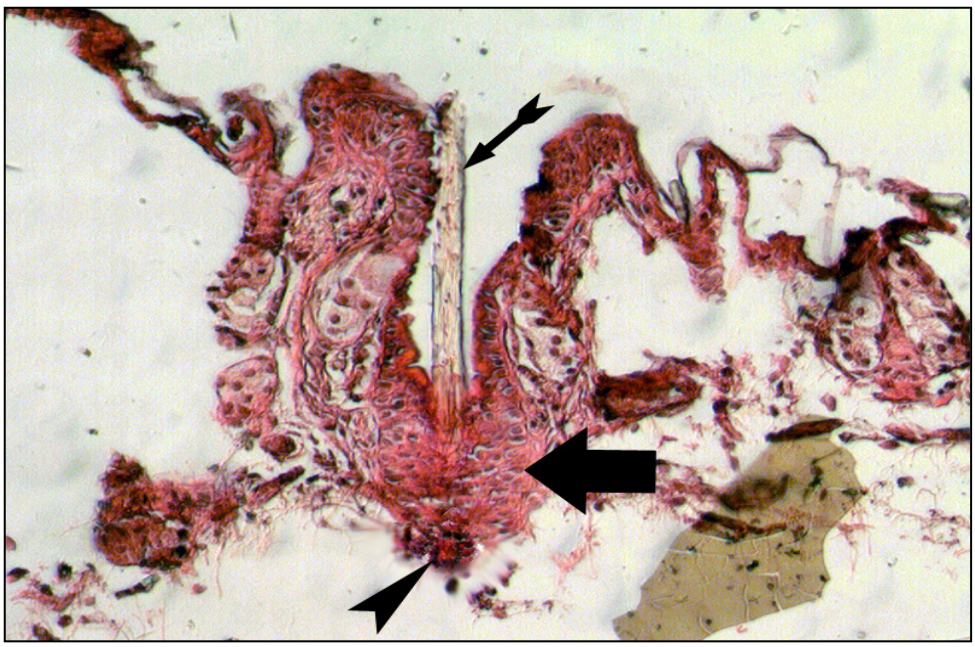

Figure 6. The skin mice treated with GH, showing a telogen hair follicle with a condensed small dermal papilla (arrow head) attached to the superficial hair bulb by the secondary germ capsule (thick arrow). Note the thin brittle hair shaft (tailed arrow). H&E X400

Table 2. The hair bulb diameter (µm) and hair follicle depth (µm) in albino male mice treated with GH and their corresponding controls (Data represent Mean±Standard deviation)

Animal group	Hair bulb diameter (µm)	Hair follicle depth (µm)
Treated	121±11.7	894±22.1
Control	76±9.4	513±16.4
P-value	<0.05	<0.05

DISCUSSION

The results of the current study clearly indicate that GH induces changes in hair growth and cycling. GH acts by two mechanisms or pathways to induce these changes: direct effects exerted by GH itself and indirect effects via GH mediator, the insulin-like growth factor-1 (IGF-1).

GH may exist in two polypeptide isoforms (isoform 1 and 2) that are considered members of the class-I cytokine family.[9] Considered as such, it may have two important effects in regard to hair growth and cycling. First, it promotes angiogenesis and vasodilatation which increases the blood flow to the growing hair follicles.[10] Increased blood flow improves cell growth and differentiation. Since anagen phase is a proliferative phase that requires increased blood flow, this effect of GH is beneficial in promoting and prolonging this phase as was seen in the treated animals in the current study. Second, GH has antiapoptotoic effects mediated by the GHR type I which is expressed by many cell types including cells of the epidermis, hair bulb and dermal papilla. This effect is mediated by the IL-3 chemical messaging cascade.[11] Anagen ends and catagen starts when the external root sheath shrinks by apoptosis during the ascent of the hair root to the bulge. The inhibition of this apoptosis by the IL-3-mediated GH action may have resulted in prolonged anagen phase in treated animals.

There is a lot of evidence indicating that growth hormone may indirectly regulate skin and hair growth and collagen synthesis via the effects of IGF-1 on the stem cells and the dermal papilla.[12] IGF-1, its receptors (IGF-1R) and its binding proteins (IGFBP) are found at high concentrations in the dermal papilla of hair follicles and they are thought to mediate the androgen-induced follicular cell growth.[13] GH increases the expression of IGF-1 mRNA and results in increased hair growth and length.[14] In the current study, the greater bulb diameter and depth may represent the histological manifestations of the effects of IGF-1 whose synthesis is triggered by GH. The hair cycle altering effect of IGF-1 may be related to its autocrine/paracrine actions on the proliferation of epithelial cells in the follicle bulb since it has morphogenic and mitogenic properties that affect the differentiation of hair follicles.[15] It has been shown that IGFBP-3, which is the most abundant type of IGFBP in dermal papilla cells, forms a complex with free IGF-1 that maintains the anagen phase.[16] IGF-1 has been found to stimulate human hair growth *in vitro* at physiologic concentrations and to prevent the premature entry of cultured hair follicles into catagen.[17] All these facts support the findings presented in this study as an indirect action of GH via the expression of IGF-1.

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پوختە

هورمونێ گەورەبوونێ کارتیکرنێ لسەر گەورەبوونا پرچی دکەت و گوهرینا خولی ل پرچی دگەت ل مشکێن سپی: ڤەکولینەکا هستولوجی

پێشەکی و ئارمانج: گوهرینێن بەردەوام چێدبن ل پرچی ل دەمێ گەورەبوونێ د ئیپیتلیەم و پێستی دا. هورمونێ گەورەبوونێ دبیت رولەکێ کارتیکەر هەبیت لسەر مەشکولێن پرچی. ئەڤ ڤەکولینە هاتە کرن ژ بو هەلسەنگاندنا کارتێکرنێن هورمونێ گەورەبوونێ لسەڤ مەشکولێن پرچی ل مشکێن سپی بێن نێر.

ریکێن ڤەکولینێ: هورمونێ گەورەبوونێ هاتە دان لبن پێستی بو 10 مشکێن سپی بێن نێر ئێك قوم یا 5 ملگم/کیلوگرام بو ماوێ 4 حەفتیا. هەلسەنگاندنا رولێ وێ لسەر گەورەبوونا پرچی هاتە کرن ب رێکا پیڤانا درێژاهیا پرچی، هستولوجیا مشکولێن پرچی، کیراتیا پرچی دناڤ پێستی دا، فرەهیا پیڤازوکا پرچی و هاتە بەرەوارگردن دگەل 10 مشکێن ددی بێن هورمون بو نەهاتیە دان.

ئەنجام: ئەو مشکێن خورمون وەرگرتین پرچێ وان درێژ بوو و مەشکولێن پرچی زێدەبوون ل بارێ (anagen) و هەروەسا کیرتر دناڤ پێستی دا دگەل مەزنبوونا پیڤازرکا پرچی مشکێن کونترول پتر رێژا مەشکولی ژ بارێ (categen) دا هەبوون.

دەرئەنجام: هورمونێ گەورەبوونێ رولەکێ گرنك یێ هەی د گەورەبوونا مەشکولێن پرچی. ئەڤ هورمونە کارتێکرنێ دکەتە لسەر خولا پرچی و رولەکێ (antiapoptotic) یێ هەی کو دەمێ بارێ (anagen) درێژکەت و دەمێ بارێ (categen) کورتکەتن.

الخلاصة

هرمون النمو يؤثر على نمو الشعر و يعدل في التغيرات الدورية لنمو الشعر في ذكور الفئران البيض: دراسة نسيجية

خلفية واهداف البحث: يخضع نمو الشعر و تطوره لتغيرات دورية تنطوي على إعادة تشكيل سريعة للمكونات الجلدية و الظهارية، و يلعب التحفيز البيخلوي للجزيئات البيخلوية دورا مهما في هذه العملية. و قد يؤدي هرمون النمو دورا أساسيا في نمو و تغير بصيلات الشعر من خلال تأثيره على هذه الجزيئات، لذلك كان من الجوهري الإلمام بمسارات هذه الجزيئات و تأثير هذا الهرمون عليها لما له من أهمية في تحقيق الأهداف العلاجية لأمراض الشعر المختلفة ، صممت هذه الدراسة لبحث آثار هرمون النمو على نمو بصيلات الشعير و التغيرات الدورية التي تحدث فيه.

طرق البحث: تم حقن عشرة من الفئران البيض بجرعة 5 مغ/كغ من هرمون النمو تحت الجلد لمدة 4 أسابيع و على شكل جرعة واحدة يوميا، ثم درست آثار هذه الجرعة على نمو الشعر من خلال قياس طول الشعر الملتقط و دراسة بصيلة الشعر و مرحلة نموها نسيجيا و قياس عمق و قطر جريب الشعرة في منطقة من الجلد محضرة بنزع الشعر كيميائيا في وقت سابق. تم مقارنة النتائج مع عشرة من فئران البيض التابعة لمجموعة السيطرة.

النتائج: أظهرت الحيوانات المعالجة زيادة في طول الشعر الملتقط و زيادة في النسبة المئوية لبصيلات الشعر في مرحلة طور التنامي مع زيادة في عمق و قطر جريبات الشعر، بينما أظهرت حيوانات مجموعة السيطرة نسبة مئوية أعلى لبصيلات الشعر في مرحلة طور التراجع.

الاستنتاجات: يلعب هرمون النمو دورا مهما في تطور نمو بصيلات الشعر و إدامتها و يتميز بخصائص مضادة لاستماتة الخلايا تعمل على إطالة فترة طور التنامي للشعرة و تأخير طور التراجع.

FREQUENCY OF LEFT VENTRICULAR SYSTOLIC DYSFUNCTION IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE PATIENTS

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Submitted 2 May 2011; accepted 3 Dec 2011

ABSTRACT

Background and objectives To determine the frequency of left ventricular systolic dysfunction in chronic obstructive airway disease patients and its relation to age, gender, duration of smoking and other factors.

Methods A case series study of forty two chronic obstructive airway disease patients (mean age 63.64±10.21 years) were studied for assessment of left ventricular systolic dysfunction using 2D and M-mode echocardiography with assessment of ejection fraction for all patients. Assessment of clinical parameters and biochemical parameters. The age and gender of the patients were assessed. Duration of smoking and the number of pack per year were also calculated. The study was carried out in the respiratory care unit and general medical units of Ibn-Sina Teaching Hospital.

Results Forty two chronic obstructive airway disease patients 36 males (85.7%) and 6 (14.3%) females (mean age 63.64±10.21 years), were studied for assessment of left ventricular ejection fraction. Among the 42 patients only 9 (21.4%) had left ventricular ejection fraction with 2(22.2%) among females and 7 (77.8%) among males, (p= 0.382), The Mean age of left ventricular ejection fraction group was found to have no significant correlation at (p=0.442). Age compared with the groups of left ventricular ejection fraction, this correlation was not significant (p=0.267). The mean duration of smoking and pack years showed no significant association with left ventricular ejection fraction (p=0.618 and p=0.348 respectively). Patients characteristics show no sensible statistical correlation to LVSF (p =0.338), (p =0.42, p =0.26), (p=0.163, p=0.288, p=0.463) in sequence.

Conclusions The frequency of left ventricular systolic dysfunction in chronic obstructive airway disease patients was 21.4 %. Age, duration of smoking and pack years in addition to other patient's characteristics didn't demonstrate a significant relation to left ventricular systolic function in chronic obstructive airway disease patient. More sophisticated tools should be used for evolution of left ventricular systolic dysfunction in chronic obstructive airway disease patients.

Duhok Med J 2011;5(2): 51-59.

Key words: Systolic dysfunction, Ejection fraction, COPD

The most common causes of left ventricular systolic dysfunction (LVSD) are coronary heart disease, idiopathic dilated cardiomyopathy, hypertension, and valvular heart disease. Effective therapy for hypertension has led to a changing pattern in which coronary heart disease has become more prevalent as a cause of heart failure than hypertension. The left ventricular ejection fraction (LVEF) is expressed as the ratio of the stroke volume divided by the end-

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diastolic volume.

Several non-invasive bedside techniques can provide useful information without the associated procedural risks like biplane contrast left ventriculography. Some of the non-invasive approaches have even a better accuracy and reproducibility of LVEF measurements than the invasive techniques as claimed by some study.[1]Two dimensional echocardiography allows real-time imaging of the heart and its various structures using ultrasonic waves. Several imaging windows, including parasternal, apical, and subcostal views, are used to visualize all ventricular walls.[1]

Chronic obstructive pulmonary disease (COPD) defined by the Global Initiative (GOLD) , as a disease state characterised by airflow limitation that is not fully reversible. The ratio of forced expiratory volume in one second divided by forced vital capacity (FEV1/FVC) <70% even after bronchodilator therapy.[2]The FEV1 and the FEV1/FVC ratio fall progressively as the severity of COPD increases. Up to 30 percent of COPD patients have an increase of 15 percent or more in their FEV1 following inhalation of a beta-agonist aerosol.[3]
Evidence of airway obstruction and a bronchodilator response on pulmonary function tests is found not only in COPD but also in acute congestive heart failure therefore it's important to differentiate between them.[4,5]

The frequency of erythrocytosis increases as arterial PO_2 falls below 55 mmHg and this is the case in COPD. The response of the bone marrow to hypoxemia is complex, resulting in a variable relation between blood oxygen level and red cell mass in COPD.[3] The European Society of Cardiology (ESC) defined heart failure as clinical symptoms and objective evidence of cardiac systolic and/or diastolic dysfunction. Left ventricular systolic dysfunction (LVSD) was defined as a LVEF <50% assessed by echocardiography.[6]

Most of patients who develop left ventricular failure do so as a consequence of systolic left ventricular dysfunction (SLVD) related to hypertension and or coronary atherosclerosis, conditions that share risk factors with COPD, particularly tobacco use.[7] Epidemiologic studies confirm the relatively frequent coexistence of COPD and coronary artery disease.[8]

COPD may obscure clinical signs of coexisting LVD. Both disorders produce similar symptoms like paroxysmal nocturnal dyspnoea, orthopnea, and cough.[9,10]

The first studies that reported diastolic dysfunction was based on interventional catheterization.[11,12] They were confirmed by experimental research in animals, and in humans using Doppler ultrasound.[13,14]

According to these studies, the frequency of abnormalities in left ventricle relaxation has been suggested to be present in nearly 90% of patients with COPD. Doppler studies for the diastolic function have been studied by the combined analysis of mitral and pulmonary venous flow, and the evaluation of the filling pressure.

In COPD chronic hypoxemia can lead to myocyte hypoxia with intracellular calcium transport disturbances.[15,16] Pulmonary hypertension commonly ensue with right ventricular pressure overload.These may lead to right ventricular hypertrophy in COPD patients and by time the right ventricle dilates.[15,17,18]

During diastole the left ventricle circular configuration becomes distorted due to the displacement of the ventricular septum toward the left ventricular cavity secondary to right ventricular pressure overload.[19] All these changes will lead to LVSD.

The aim of this study is to determine the frequency of left ventricular systolic dysfunction in COPD and its relation to age, gender, duration of smoking and other factors.

METHODS

During the period from the first of May 2009 to end of December 2009, 42 COPD patients (all of them were already diagnosed by clinical means and pulmonary function tests). Thirty six (85.7%) males and 6 (14.3%) females were included with a mean age 63.64±10.21 years were studied for assessment of left ventricular systolic function (LVSF) at Ibn Sina Teaching Hospital wards and respiratory care unit.

Exclusion criteria were: the presence of hypertension, ischemic heart disease (detected by history and clinical examination, surface electrocardiogram, and or left ventricular wall abnormalities during echocardiographic examination), cardiac arrhythmias, congenital or acquired valvular heart disease and diabetes mellitus.

Proper history and clinical examination were performed for all patients at the bed side to assess the patient clinical state. The measurements of personal attributes, fasting blood glucose, haemoglobin, blood urea and chest x-ray were performed in all cases. Smoking habits and its duration and current medical treatment were carefully recorded with calculation of body mass index (BMI).

According to the American society of echocardiography guidelines and standards, all the patients underwent echocardigraphic examination by using 2D M-mode to evaluate the ejection fraction (EF) % as criteria for diagnosing impaired relaxation.

Furthermore the pseudonormalised patients that cannot be diagnosed by transmitral flow Doppler alone were studied by combining the float, and was considered abnormal if the EF was <50.[20]

LVSF was divided into two groups LVSD positive and LVSD negative.

Age groups were divided into four groups (40 - 50 years), (51 - 60 years), (61- 70 years) and (71 - 80 years), and then compared to the level of LVSF. The duration of the illness was grouped as more than 30years and less than 30 years, and then compared to the level of LVSF. Pack year smoking calculated. Patients smoked 10 pack years means 20 cigarettes smoking/day for 10 years. Body mass index as $\geq$30 kg/m^2 or <30 kg/m^2.

The analysis was done by using spss software version.[16] All categorical variables were expressed as counts percentages and were compared with Chi square test or Fisher's exact test when appropriate. The mean $\pm$ SD was calculated for all continuous variables. P value < 0.05 was considered statistically significant.

RESULTS

Forty two COPD patients of whom 36were male (85.7%) and 6 (14.3%) were females (with mean age 63.64±10.21 years) were studied for assessment of LVSF.

Among the 42 patients, only 9 (21.4%) had systolic dysfunction; 2 (22.2%) were female patients and this number comprised one third of the female patients in the sample studied. The males form 7 (77.8%). The correlation between gender and LVSF was not statistically significant (P= 0.382), (Table 1).

Table 1. Gender and its correlation to the left ventricular ejection fraction

Gender	EF% > 50% No. (%)	EF% ≤50% No. (%)	p-value
Female	4 (12.1)	2 (22.2)	0.382*
Male	29 (78.9)	7 (77.8)	
Total	33 (100)	9 (100)	

** Non significant result*
EF: Ejection fraction

The Mean age of (males and females) was found not significantly different amonge LVSF group (p=0.442), (Table 2).The age of patients were classified according to gender into four groups, then compared to the groups of LVSF. Again this correlation was not significant (p=0.267), (Table 2).

Table 2. Age groups compared to left ventricular ejection fraction

Age	LVSD		p-value
	Negative N=33	Positive N=9	
Mean ±SD	63.00±10.98	66.00±6.70	0.442*
40-50 (%)	6(18.2)	0(0.0)	0.267*
51-60 (%)	4(12.1)	3(33.3)	
61-70 (%)	12(36.4)	4(44.4)	
71-80 (%)	11(33.3)	2(22.2)	
	33(100)	9(100)	

**non significant result*
LVSD: left ventricular systolic dysfunction

The mean duration of smoking and pack years showed no significant association with LVSD (p=0.618) and p=0.348 respectively, (Table 3).

Patients characteristics demonstrated in table 4 showed no significant statistical correlation between LVSF with BMI, pulse rate, respiratory rate haemoglobin and blood urea (p=0.338, p=0.42, p=0.26), (p=0.163, p=0.463 respectively)as shown in table 4.

Table 3. Duration of smoking and pack years in comparison to left ventricular ejection fraction

		LVSD		P-value
		(-)	(+)	
Duration of smoking	mean±SD	34.33%±14.82	40.66±10.40	0.234*
	<30 years	5 (12.2)	1 (11.1)	0.618*
	≥30 years	28 (84)	8 (88.9)	
Pack year smoking	Means ±SD	34.54±12.01	38.55 ±9.01	0.358*
	<10	3 (9.17)	0	
	≥10	30 (90.9)	9 (100)	0.348*
Total No. (%)		33 (100)	9 (100)	

**non significant result*

Table 4. Patients characteristics in relation to left ventricular ejection fraction

Patients Characteristics		LVSF		P-value
		Negative N=33 (%)	Positive N=9 (%)	
BMI	<21	10 (30.13)	4 (44.45)	0.338*
	≥21	23 (69.7)	5 (55.6)	
PR	<100	33 (100)	7 (77.8)	0.42*
	≥100	0	2 (22.2)	
RR	<25	32 (97)	6 (66.7)	0.26*
	≥25	1 (3.0)	3 (33.3)	
HB	<16	26 (78.8)	5 (55.6)	0.163*
	≥16	7 (21.2)	4 (44.4)	
Blood urea	>6.1	19 (57.6)	6 (66.7)	0.463*
	<6.1	14 (42.1)	3 (33.3)	

**non significant result*

DISCUSSION

Cardiovascular deaths are accounted for about 20%-25% of the mortality cases throughout all stages in COPD patients.[21]

This study demonstrates that the frequency of LVSD among COPD patients were 21.4%. These results were in the same line of Fransih et al.[22]

These data are in support of the hypothesis that "hypoxia and the excess accumulation of toxic metabolic products like lactic acid, significant right to left shunting through the bronchial circulation explains the diminished LVEF in COPD patients".[23] It was estimated in recent study that for every 10% decrease in forced expiratory volume in one second (FEV1), all cause mortality increases by 14%, cardiovascular surgery (CVS) mortality increases by 28%, and non-fatal coronary events increase by 20 %.[24]

The explanation of the low frequency of LVSD in COPD patients who use inhalation of long acting β2-adrenoreceptor agonists as part of the treatment in COPD is mostly due to the fact that these drugs are more quickly removed from myocardial and kidney receptors, [25] this will make the potentially deleterious cardiac side effects less likely. This can be used to explain why the LVSD is not too frequent in our studied sample.

Our finding in this study was statistically not significant, which may be due to the fact that the study sample included only the selected patients as mentioned earlier by the exclusion criteria.

Furthermore other studies had found approximately the same results but in the absence of the exclusion criteria which we used as they were nonselective.[26,27,28] These studies show more clearly the effects of co morbidities of COPD and left ventricle on the results of LVSF.

The Mean age of patients were found to have nonsignificant relation to LVSD. The absence of relationship was explained by Alain et al.[29] Regarding the gender and its relation to LVSF in the current study, there was no statistically significant difference between females and males and this goes with the findings of Alain et al.[30] The mean of pack years smoking was 35.40±11.45 and the percentage of LVSD positive patients with pack years < 10 was 0% while in ≥ 10 was 100%.These results confirms the association of pack years smoking with development of LVSD although the mean duration of smoking and pack years showed no significant association with LVSD.

The BMI percentage as a mean for evaluation of adiposity in LVSD positive patients was 44.45% in whom the BMI was <21, while it was 55.6% in those ≥ 21.Similar finding was found by Alain, et al.[30]

The heart rate and respiratory rate showed no significant association with LVSD.

It is recommend that patients with COPD should have echocardiographic assessment to rule out an underlying LVD. Transmitral flow Doppler, tissue Doppler and venous flow Doppler should be used for better evaluation of myocardial function in COPD patients.

In conclusion the frequency of LVSD in COPD patients was 21.4 %. Age, duration of smoking and pack years in addition to other patient's characteristics did not demonstrate a significant relation to LVSF in COPD patients. More sophisticated tools should be used for evaluation of LVSD in COPD patients.

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پوختە

ڕێژا خراب کارکرنا سیستولی یێ زگوڵاً دلی یا چەپێ ل نەخوشێن تووشی نەخوشیا سییەکی بێن کون گرتنێ دوم درێژ بووین

پێشەکی و ئارمانج: ئەڤ ڤەکولینە هاە کرن ژ بو دەستنیشانکرنا ڕێژا خراب کارکرنا سیستولی یێ زگوڵاً دلی یا چەپێ ل نەخوشێن تووشی نەخوشیا سییەکی بێن کون گرتنێ دوم درێژ بووین و پەیوەندیا وێ دگەل تەمەنێ نەخوشی، ڕەگەز، ماوێ جگارەکێشانێ و هندەك فاکتەرێن دی.

ریکێن ڤەکولینێ: زنجیرەکا حالەتا کو پێکهاتی بوو ژ 42 نەخوشێن تووشی نەخوشیا سییەکی بێن کون گرتنێ دوم درێژ بووین (63.64±10.21) سال هاتنە وەرگرتن ژ بو دیارکرنا کارکرنا سیستولی یێ زگوڵاً دلی یا چەپێ ب کارئینانا ئیکو یا دلی ژ جورێ (2D and M mode) و دیاکرنا ڕێژا فرێدانا خوینێ ژ دلی بو هەمی نەخوشا و هەروەسا چەند پارامیترێن دی بێن کلینیکی و بایوکیمستری هاتنە وەرگرتن دگەل ژیێ نەخوشی، ڕەگەز، ماوێ جگارەکێشانێ و کا چەند جگارە کێشاینە د سالێ دا. ئەڤ حالەتە هاتنە وەرگرتن ژ بەشی سییەکی و بەشێ هناڤا ل نەخوشخانا ابن سینا یا فێرکرنێ.

ئەنجام: 42 نەخوش بێن و توشی نەخوشیا سییەکی بێن کون گرتنێ دوم درێژ بووین، 36 ژ ڕەگەزێ نێر (85.7٪) و 6 ژ ڕەگەزێ مێ (14.3٪) کو ژیێ وان 63.64±10.21 سال بوون هاتنە وەرگرتن. ب تنێ 9 نەخوش (21.4%) خراب کارکرنا سیستولی یێ زگوڵاً دلی یا چەپێ هەبوون، 2 (22.2%) مێ بوون و 7 (77.8%) نێر بوون. تەمەن و ژمارا جگارەکێشانێ چێ پەیوەندییێن ستاتیستیکی نەبوون دگەل کارکرنا سیستولی یێ زگوڵاً دلی یا چەپێ.

دەرئەنجام: ڕێژا کارکرنا سیستولی یێ زگوڵاً دلی یا چەپێ ل نەخوشێن تووشی نەخوشیا سییەکی بێن کون گرتنێ دوم درێژ 21.4٪ یە. تەمەن، دەمێ و ژمارا جگارەکێشانێ دگەل هندەك فاکتەرێن دی چێ پەیوەندی نەبوون دگەل دگەل کارێ سیستولی یێ زگوڵاً دلی یا چەپێ ل نەخوشێن تووشی نەخوشیا سییەکی بێن کون گرتنێ دوم درێژ بووین. ئامیرێن پتر پێشکەفتی دڤێن بهێنە یکارئینان ژ بو هەلسەنگاندنا خراپ کارکرنا سیستولی یێ زگوڵاً دلی یا چەپێ ل تووشی نەخوشیاسییەکی بێن کون گرتنێ دوم درێژ بووین.

الخلاصة

تواتر ضعف البطين الأيسر الانقباضي المزمن عند مرضى انسداد مجرى المسالك التنفسية المزمن

خلفية واهداف البحث: تحديد تواتر خلل البطين الأيسر الانقباضي في مرضى انسداد مجرى المسالك التنفسية المزمن، وعلاقته بالعمر والجنس للمرضى ودراسة تاثيرمدة التدخين وعوامل أخرى على هذا الفحص.

طرق البحث: تم دراسة 42 مريضا يعانون من مرض انسداد مجرى المسالك التنفسية المزمن ،متوسط أعمارهم (63.64± 10.21سنة)، لتقييم خلل البطين الأيسر الانقباضي، وذلك باستخدام (D2 and M Mode) مع تقييم معلمات الكيمياء الحيوية والفحوصات السريرية ومتغيرالعمر .جرى تقييم المرضى من الجنسين. وتم احساب تاثير مدة التدخين. أجريت الدراسة في وحدة العناية التنفسية والوحدات الطبية العامة لمستشفى ابن سينا،وقد تم احتساب تاثير هذه المتغييرات مع وظيفة البطين الأيسر الانقباضي. تم إجراء التحاليل الإحصائية بواسطة برنامج (SPSS 16) تم استخدام اختبار كاي سكوير بالاضافة الى اختبار ANOVA حسب الحاجة، وتعتبر قيمة (P <0.05) ذات دلالة إحصائية معنوية.

النتائج: تم دراسة اثنين وأربعين مريضا يعانون من مرض انسداد مجرى المسالك التنفسية المزمن. 36 ذكور (85.7٪) و 6 (14.3%) إناث. متوسط اعمارهم 63.64 ± 10.21 سنة. لتقييم خلل البطين الأيسر الانقباضي بين المرضى بينت النتائج ان من بين 42 مريض سوى 9 (21.4%) يعاني من خلل البطين الأيسر الانقباضي مع 2 (22.2٪) من بين الإناث و 7 (77.8%) من بين الذكور وكانت قيمة الارتباط (P= 0.382). متوسط اعمار مجموعة خلل البطين الأيسر الانقباضي ليست ذات ارتباط معنوي كبيرة (P= 0.442). العمرو مقارنة مع مجموعات مرضى خلل البطين الأيسر الانقباضي ، ليست ذات ارتباط معنوي كبيرة P= 0.267. التدخين لم تظهر له أي ارتباط معنوي ايظا مع (P= 0.348) على التوالي. خصائص المرضى لم تظهر أي علاقة معنوية احصائية = 0.338)، 0.26 = (ع = 0.42، P) ، ع (= 0.163، P = 0.288، P = 0.463) على التوالي.

الاستنتاجات: تواتر خلل البطين الأيسر الانقباضي عند مرض انسداد مجرى المسالك التنفسية المزمن كان 21.4 ٪. من المرضى، مدة التدخين عمر المرضى بالاضافة الى عمر وجنس المرضى لم تثبت وجود علاقة معنوية كبيرة مع LVSF عند مرضى انسداد مجرى المسالك التنفسية المزمن. وينبغي استخدام أدوات أكثر تطورا لفحص LVSD في المرضى الذين يعانون من انسداد مجرى المسالك التنفسية المزمن.

POSTCARDIAC SURGERY PERICARDIAL TAMPONADE

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Submitted 29 May 2011; accepted 3 Dec 2011

ABSTRACT

Background and objectives Post cardiac surgery pericardial tamponade is amongst the most lethal post open heart surgery complication. It represents a challenging task for surgeons as they need a rapid and accurate assessment and management. The objectives were to focus on this very fatal complication to analyze the patients who develop this complication with revealing the most risk factors, showing its incidence and mortality.

Methods This is a cross sectional study of 25 consecutive patients developed cardiac tamponade postoperatively in Ibn Al-Bitar Hospital for Cardiac Surgery from January 2004 - June 2005. The patients are divided into two groups according to the time of development of tamponade after surgery into early 44%, and late 56%.

Results Early tamponade occurred more commonly among the patients underwent coronary artery bypass grafts coronary artery bypass grafts surgery while late tamponade were common after valve surgery, with the use of anticoagulants and prolonged prothrombin time. The overall mortality in patients who developed tamponade was 12% which is due to delay in pericardial decompression.

Conclusions Our mortality rate due to this complication is still high mostly due to delay in diagnosis which need to draw more attention to reduce it as much as possible.

Duhok Med J 2011;5(2): 60-68.

Key words: Tamponade, Pericardium, Pericardiostomy, Pericardiocentesis

Cardiac tamponade is a life-threatening, slow or rapid compression of the heart due to the pericardial accumulation of fluid, blood, clot, pus or gas as a result of effusion, trauma (traumatic tamponade is most common following cardiac surgery.[1] William Harvey (1649) the first who described a case of hemopericardium.[2] Franz Schuh performed the first blind pericardiocentesis in 1840.[3]

Normal pericardial pressure varies between +5 and -5 cm H_2O and equals the pleural pressure.[4] Patient may acutely accumulate a small amount of pericardial fluid with a big increase in pressure. Conversely, the slow development of a large chronic pericardial effusion may produce negligible hemodynamic consequences. It is very important to recognize that the pericardial fluid volume and pericardial pressure are not linearly related (Figure 1).[3]

Critical tamponade is a form of cardiogenic shock which may preceded by symptoms like chest discomfort and pleuritic pain, tachypnea and dyspnea on exertion that progresses to air hunger, anorexia and cough. The slow accumulation of pericardial clot may present quite differently so the diagnosis of cardiac tamponade following cardiac surgery requires a great deal of clinical judgment because the patient may have cardiac deterioration from ventricular failure as well as compressive disorders and the surgeon must determine which factors are responsible.[2] Beck's triad (hypotension, distended neck veins, and muffled heart sound) is the classical

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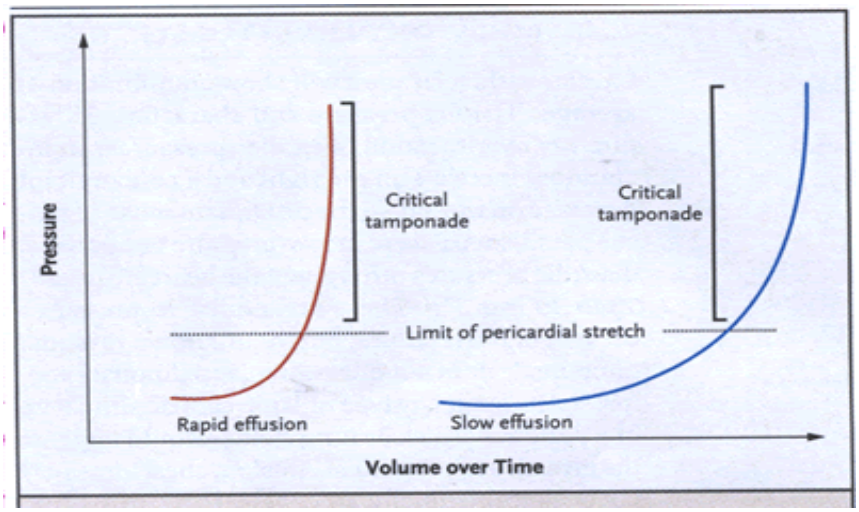

Figure 1. The pericardium showing changes in the pericardial pressure and volume in rapidly and slowly developed pericardial effusion (Source: Baue et al[3])

finding of pericardial tamponade,[5] absolute or relative hypotension; in rapid tamponade, patients are often in shock, with cool arms and legs, nose, and ears and sometimes peripheral cyanosis.[1] diminished urine output should alert the surgeon to the possibility of ongoing cardiac tamponade.[2] Although it might occur in other conditions a key diagnostic finding, pulsus paradoxus conventionally defined as an inspiratory systolic fall in arterial pressure of 10 mm Hg or more during normal breathing, is often palpable in muscular arteries.[1] An electrocardiogram may show signs of peri-carditis, but the only quasi specific sign of tamponade is electrical alternation (Figure 2).[6] Chest radiography findings include enlarged cardiac silhouette (Figure 3).[6]

Echocardiography shows the following findings when intrapericardial pressure increases above the right ventricular cavity pressure (Figure 4): (i) Size of pericardial effusion; (ii) increased dimension and decreased inspiratory collapse of inferior vena cava; (iii) early diastolic collapse of right ventricular outflow tract, happens because during early diastole the intraventricular pressures fall below the intrapericardial pressure. As right ventricular outflow tract is thin, it collapses during early diastole.[7]

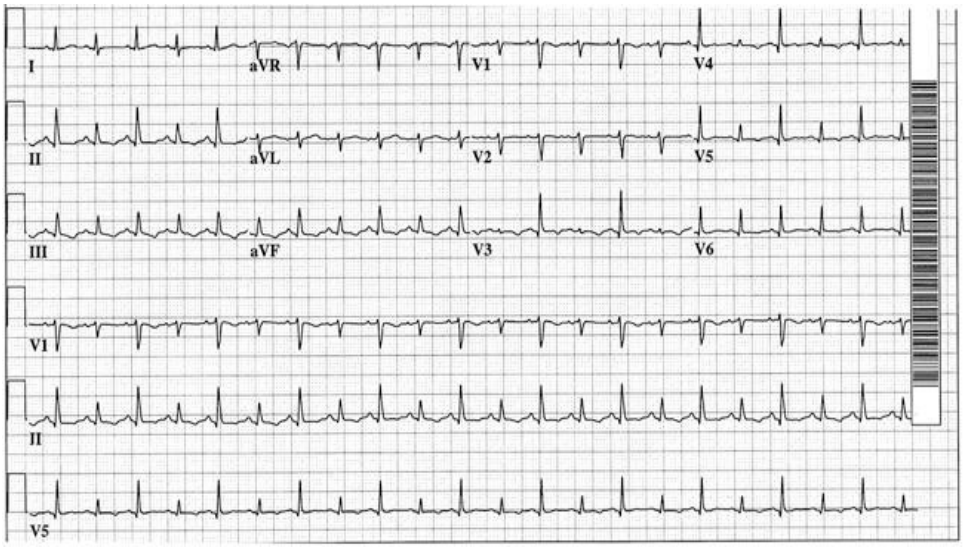

Figure 2. Twelve-lead electrocardiogram shows electrical alternans. Note the alternating amplitude and vector of the P waves, QRS complexes, and T waves (Source: Lau et al[6])

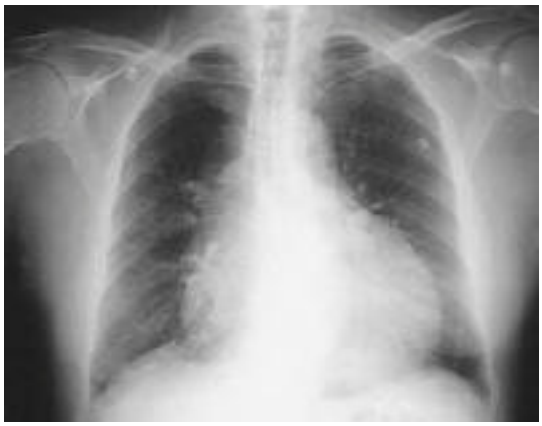

Figure 3. "Water-bottle" appearance of the cardiac silhouette) (Source: Lau et al[6])

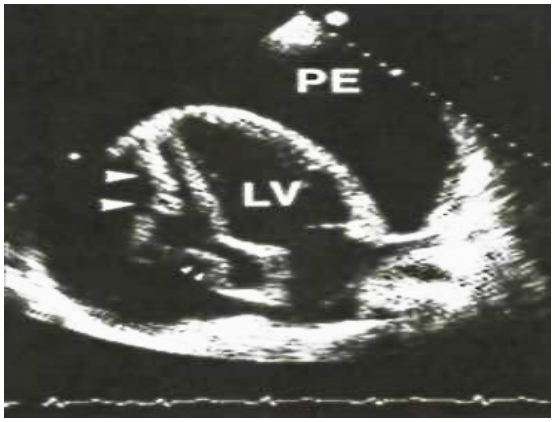

Figure. 4 large pericardial effusion (PE), right ventricular wall collapse (large arrows) right atrial wall collapse (small arrows) consistent with tamponade, LV= left ventricle (Source: Mittal[7])

Several techniques are used in the management of acute cardiac tamponade: Pericardiocentesis which is a diagnostic and therapeutic procedure performed through a subxiphoid or trans-thoracic approach[8]; pericardiostomy using subxiphoid pericardial window; Sternotomy with re-exploration of patient in early post-operative period good homeostasis and reclosing the sternum and incision done accordingly.[9]

METHODS

This is a case series study of 25 patients out of 654 patients underwent open heart surgery who developed pericardial tamponade postoperatively in Ibn-Al-Bitar Hospital for cardiac surgery from January 2004 through June 2005. Some patients were diagnosed as cardiac tamponade on clinical bases in the intensive coronary unit (ICU) in early postoperative period and re-exploration done either in the intensive care unit or in the theater. Other patients were discharged and then presented again with significant hemodynamic compromise they were re-admitted to hospital clinically evaluated and confirmed by echo study, combined with other complementary investigations, where hematological, biochemistry, prothrombin time (PT) and international normalized ratio (INR) were checked, and if it is severely prolonged fresh frozen plasma given with repeated checking of PT and INR 1 or 2 pints of whole blood is prepared and emergency pericardiostomy or pericardiocentesis were done and usually the patients discharged within 48 to 72 hrs.

Three types of surgical procedure were done in patients with pericardial tamponade. Pericardiostomy it was done in 11 cases and sternotomy (re-exploration) was done in 12 cases. Pericardiocentesis was done in 2 cases.

Operative findings,13cases hemorrhagic fluid (no ooze, no identified site of bleeding, 8 cases oozing from whole raw area, 4 cases with identified site of bleeding The types of pericardial fluid: (Hemorrhagic fluid in 13 cases, Fresh blood in 6 cases, Clot in 6 cases) and no negative exploration. The total number of the open heart surgeries done during the period of the study was 654 cases.

RESULTS

The data identifies two groups of patients classified according to the time of tamponade development from the time of surgery as shown in table 1.

The relationship of tamponade with the type of most common surgical procedures done in our hospital (CABG, valvular and congenital) will be shown in table 2.

Table 1. Classification of postcardiac surgery tamponade according to the time of development

Group	Time of tamponade	No.
I	Early, hospital stay (within 7 days).	11
II	Late, after patients discharged from hospital	14
Total		25

Table 2. Types of open heart surgery and incidence of tamponade

Type of surgery	Valvular No. (%)	Congenital No. (%)	CABG No. (%)	Other* No. (%)	Total No. (%)
No.	300 (46)	188 (29%)	143 (22%)	23 (3%)	654
Tamponade	13 (4.3)	7 (3.7%)	5 (3.4%)	0 (0%)	25 (4%)

** Other open heart surgeries include (myxoma, pulmonary embolism, left ventricular aneurysm, trauma*

Figures 5, 6, and 7 show the relationship of factors included in the study (the type of surgery, the use of warfarin, and the prolonged INR after surgery) with the development of tamponade. The incidence of tamponade in all the three major types of surgeries seems to be near 4% but the time of development is different, the majority of patients in group II are those with valve replacement (11 cases) which constituted about 79% of all cases in group II, while in group I we have only 2 cases (18%), as shown in figure 5.

Patients with oral anticoagulant (mainly those with valve replacement) are more prone to develop late postoperative tamponade so they form the majority of group II, 12 patients (86%), as shown in figure 6.

Full hematological investigations including PT (INR) were carried out to all patients in group II, ten out of twelve patients have had an INR >= 3.5 as shown in figure 7. Coronary artery bypass grafting was found to be constituting around half of cases in group I, however congenital and valvular types were next to it 36% and 19% respectively figure 5.

When those patients were re-explored only 4 of them have had an identified site of bleeding (e.g., site of venous cannulae, slipped ligature),while in the remaining 7 no surgical cause could be seen. In group I, the mean amount of blood drained before re-exploration was 1045 ml, and mean time before re-exploration was 8 hours. One patient from each group died because of a delayed intervention; the other death was due to an issued multiorgan failure after a delayed re-exploration as shown in, mortality in group I (18%), in group II (7%) (Figure 8).

During the period of study 654 patients underwent open heart procedures with an overall mortality of 13% (52 deaths) three of them 5.8% was due to tamponade only, however these deaths constituted 12% from patients developed tamponade (25) with an overall incidence of death due to tamponade from the whole work is 0.46%, i.e. we are prone to lose one patient from tamponade, from each 200 cases underwent open heart surgery.

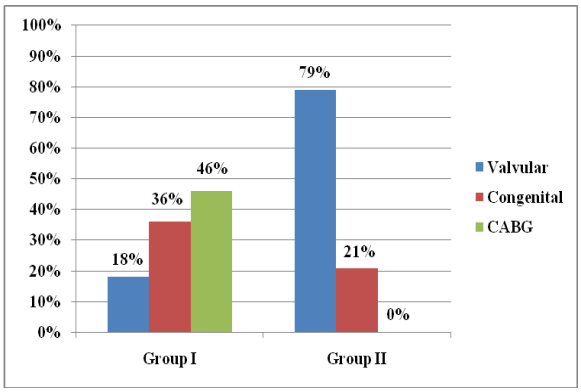

Figure 5. The relation of the type of surgery to the time of development of tamponade

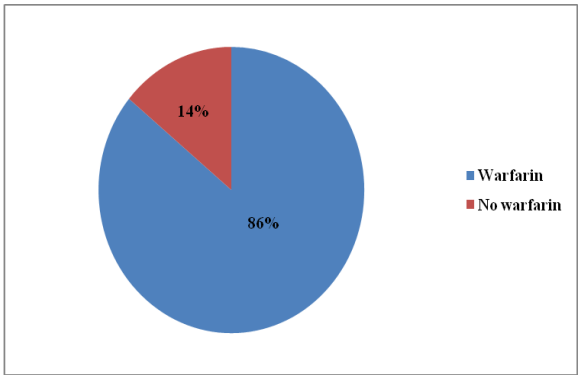

Figure 6. The relation between post surgical pericardial tamponade and warfarin

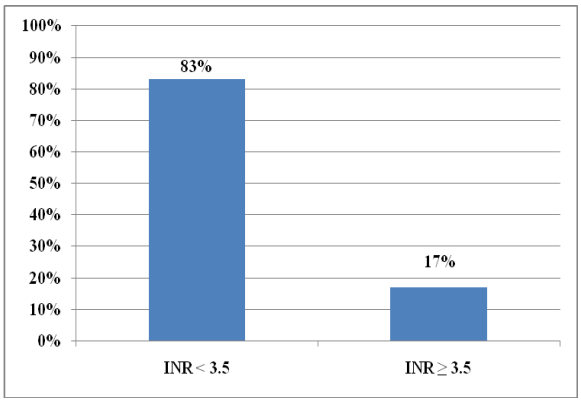

Figure 7. The relation of prolonged INR with Tamponade development

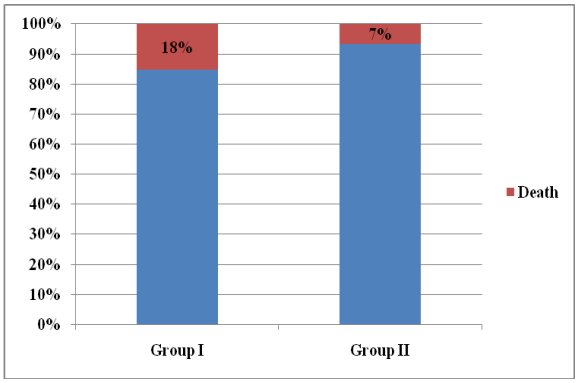

Figure 8. Mortality of tamponade

DISCUSSION

Post cardiac surgery pericardial tamponade is an anticipated, preventable and treatable event. No patient with open heart surgery is exempted from cardiac tamponade.[10]

Pericardial effusion resulting in cardiac tamponade is uncommon after open heart surgery and is associated with significant morbidity and mortality.[11] Characteristics and outcomes of patients who develop postoperative cardiac tamponade are poorly defined. Our objective was to further analyze the population at risk for developing postoperative cardiac tamponade, identify potential perioperative and surgical risk factors, and evaluate the impact of cardiac tamponade on patient outcomes. Mortality in untreated patients with cardiac tamponade is 100%,[12] but when diagnosed and treated promptly, it should significantly reduces mortality.[11] So high degree of clinical suspicion is necessary to avoid catastrophic results from missing the diagnosis of cardiac tamponade.[2] Late tamponade is a rare cause of mortality and morbidity after cardiac operation.[13] Depending on this fact, delayed intervention was the cause of our high mortality rate in this study (12%= 3 of 25). The critical question is can we help this patient by re-exploring him to evacuate the pericardial "compressive" clot? This frequent and important clinical problem has been exhaustively examined.[2] In some cases, it is much better to explore the patient for possible cardiac tamponade and risk negative results than to allow the condition to persist and cause serious morbidity[2] although no negative result was encountered in our series. CABG surgery constituted the commonest cause of early tamponade in group 1 (46%) and this may be attributed to, the activated clotting time (ACT) is not fully corrected, many anastamotic sites and More raw area during harvesting internal mammary artery. Although re-exploration in patients with CABG carries more risk because

heroic exploration may damage the grafts and/or anastamotic sites but it should be done when tamponade is suspected as a cause of the low cardiac output state and before development of permanent organ damage. In our study all patients are diagnosed on clinical base in the ICU and are re-explored in the theater or even in ICU. Late tamponade may be produced by one of the two mechanisms: hemopericardium due to over dosage of anticoagulants or an exacerbated form of the post-pericardiotomy syndrome cardiac tamponade after open heart surgery is more common following valve surgery than CABG alone.[1,11-14] It occur in variable period of time after cardiac surgery 3 days to 3 months[12]; mean 8 days after operation;[15] 18 days in another study.[13] In our study the mean time of presentation in late tamponade was 18 days after surgery. Development of undrained blood in pericardium or moderate effusion to tamponade plays a role in its pathogenesis. Again it its significantly more common after valve replacement.[15-17] Late tamponade incidence is more after valve replacement than CABG surgery (11% vs. 2%, respectively; $p< 0.01$).[10] In our study four fifth of cases are valvular and no one with CABG. Also it is higher in patients who had received anticoagulation therapy than those who had not[10] which was shown also in this study; there were 86 % of patients on warfarin and 14 % on no warfarin. The erratic response of INR was found before the diagnosis of tamponade which suggested that this response of the INR may be an early indicator of late tamponade.[18] The height INR show a higher incidence of development of pericardial effusion and/or tamponade. Frequency of late tamponade was 0.6% with mortality rate 16%.[12] Other study showed that incidence was 2.1%.[16] In our study incidence of late tamponade is about 2 % with fatality 7%. Pericardiocentesis was done in three fourths of patients with tamponade, Pericardiocentesis with catheter placement is highly effective, and patients can be reanticoagulated safely.[13] On the other hand four fifths of our patient with late tamponade underwent pericardiostomy under general anesthesia with no mortality. One case evacuated by pericardiocentesis for whom an indwelling catheter was left in pericardial cavity for 48 hours for repeated aspiration. The other case died because of a delay in evacuation of tamponade.

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پوختە

ڕێتنا خوینێ بۆ بن بەردێ دلی پشتی نشتەرگەریا دلی یا ڤەکری

پێشەکی و ئارمانج: ڕێتنا خوینێ بۆ بن بەردێ دلی پشتی نشتەرگەریا دلی یا ڤەکری ئێکە ژ پترترین (مضاعفات) ێت کوژەك ێت ڤێ جورە نشتەرگەریێ کو دبتە هەڤرکیەك بۆ نشتەرگەری، ژبەر پێویستیا ب هویربینیێ و لەزیێ د دەستنیشانکرنێ و جارەسەرکرنێ دا.

ریکێن ڤەکولینێ: ڤەکولین هاتە کرن ل سەر نموونەیەکێ ژ 25 نەخووشان ئەڤێن تووشی ڕێتنا خوینێ بۆ بن بەردێ دلی بووین وەك (مضاعفات) بوو نشتەرگەریا دلی یا ڤەکری ل نەخووشخانا ابن البیگار یا نشتەرگەرییێ دلی، هەر ژ هەیڤا کانینا دووێ سالا 2004ێ زاینی تا خزیرانا سالا 2005ێ. نەخووش هاتنە دابەشکرن ل سەر دوو گروپان ل دویف دەمێ دیاربوونا ڤی (مضاعف)ی پشتی نشتەرگەریێ، ڕێتنا بلەز" 44٪ ژ نەخووشان و ڕێتنا ڤەمایی 56٪ ژ نەخووشان.

ئەنجام: د ڤێ ڤەکولینێ دا تێبینی هاتە کرن کو پتریا نەخووشا ئەڤێن ڕێتنا بلەز ل دەف پەیدابووی نشتەرگەریا پنیکرنا خوینبەرێن تانجی کربوو، بەلێ نشتەرگەریا گوهورینا صەممایێت دلی ئەگەرێ هەرە بەربەلاڤ بوو د گروپا دووێ دا, ڕێتنا ڤەمایی, و دەرمانێت خوین روونکەر ئەڤێن دڤێرا تێنە دان. ڕێژا مرنێ پشتی کارێت ژمێریاری هاتینە کرن بۆ نەخووشێن تووشی ڕێتنا خوینێ بۆ بن بەردێ دلی بووین 12٪ بوو.

دەرئەنجام: تا ئستا ڕێژا مرنێ ژ ڕێتنا خوینێ بۆ بن بەردێ دلی یا زورە و ئەڤەژی ڤەدگەرییێت بوو ڤەمایێ د دەستنیشانکرن وجارەسەریێ دا.

الخلاصة

انصباب شغاف القلب عقابيل عمليات القلب المفتوح

خلفية واهداف البحث: انصباب شغاف القلب عقابيل عمليات القلب المفتوح واحد من أكثر المضاعفات المسببة للوفاة ويمثل تحديا للجراح لأنه يتطلب الدقة والسرعة في التشخيص والمعالجة, الهدف من البحث هو التركيز على هذا النوع من المضاعفات الذي يؤدي الى نسبة وفاة كبيرة ولتحليل المرضى الذين تعرظوا لهذا النوع من المضاعفات لبيان العوامل التي تزيد من نسبة حصوله وبيان نسبة حدوثه والوفاة الناتجة عن ذلك.

طرق البحث: تمت الدراسة على عينة من 25 مريضا تعرضوا لانصباب شغاف القلب كأحد مضاعفات عملية القلب المفتوح في مستشفى ابن البيطار لجراحة القلب للفترة ما بين كانون الثاني 2004 – وحزيران 2005 وتم تقسيم المرضى إلى مجموعتين حسب وقت ظهور هذا المضاعف من وقت أجراء العملية إلى انصباب مبكر في 44% من الحالات وانصباب متأخر في 56%.

النتائج: لوحظ من خلال هذه الدراسة إن معظم المرضى الذين اصيبوا بالانصباب المبكر كانوا قد اجروا عمليات ترقيع الشرايين التاجية في حين كانت عمليات تبديل الصمام هي السبب ألأكثر شيوعاً في المجموعة الثانية (الانصباب المتأخر) وما يرافقها من استعمال مضادات التخثر. نسبة الوفيات بعد ألأجرات ألإحصائية في المرضى الذين تعرضوا لانصباب شغاف القلب كانت 12% والذي يعزى إلى التأخر في التشخيص والمعالجة.

الاستنتاجات: لاتزال نسبة الوفاة نتيجة هذا النوع من المضاعفات كبيرة والتي يعود سببها الى التشخيص والعلاج المتاخر الذي يحتاج الى جلب الانتباه لتقليل نسبة حدوثه والوفاة الناتجة عنه.

PREVALENCE AND MOLECULAR CHARACTERIZATION OF G6PD DEFICIENT VARIANTS IN SULYMANIA PROVINCE –IRAQ

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Submitted 4 Jun 2011; accepted 3 Dec 2011

ABSTRACT

Background and objectives Glucose-6-Phosphate Dehydrogenase deficiency is the most common inherited hematological disorder among Iraqis. Studies have addressed its prevalence in several parts of the country, but neither the prevalence nor the molecular variants have been studied in the Sulymania province-northeastern Iraq. This study aimed at addressing the latter issue.

Methods A total of 838 random healthy male individuals from Sulymania province were screened for glucose-6-phosphate dehydrogenase deficiency using a fluorescent spot test. If deficient, the results were confirmed by quantitative enzyme assay. Deficient individuals with adequate samples had their DNA extracted and analyzed for four deficient molecular variants using a Polymerase Chain Reaction-Restriction fragment polymorphism method. These variants were the Mediterranean (563 C→T), Chatham (1003 G→A), A - (202 G→A), and the Cosenza (1376 G→C) variants respectively.

Results It was found that 50 individuals (6%) were glucose-6-phosphate dehydrogenase deficient. Forty of these individuals had adequate samples to analyze for the four deficient molecular variants. It was found that 30 (75%) had the Mediterranean and another 4 (10%) had the Chatham variants. No cases of A- or Cosenza variants were identified, leaving 6 cases uncharacterized.

Conclusions This study documented a 6% prevalence of glucose-6-phosphate dehydrogenase deficiency in Sulymania, an area of northeast Iraq that has not been previously studied. Furthermore, it was found that Mediterranean and Chatham variants constitute the bulk of glucose 6 phosphate dehydrogenase deficient variants in this province.

Duhok Med J 2011;5(2): 69-75.

Key words: Glucose-6-phosphate dehydrogenase deficiency, Prevalence, Mediterranean Variant, Chatham variant, Iraq

Glucose-6-Phosphate Dehydrogenase (G6PD) is an enzyme that catalyzes the first step in pentose phosphate pathway and considered the only source of NADPH and GSH in the red blood cells which are essential for defending RBCs against oxidizing agents. The gene encoding G6PD enzyme is located at Xq28, and G6PD deficiency is one of the most common enzymopathies affecting the erythrocyte metabolism worldwide.[1] Although the majority of people with

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G6PD deficiency are asymptomatic, some of the clinical symptoms associated with deficiency are acute hemolytic anemia following the ingestion of fava beans (favism) or some drugs, in association with infection or neonatal jaundice and in severe deficiency, chronic non-spherocytic hemolytic anemia.[1-3] Biochemical characterization has led to the description of no less than 442 biochemical variants of G6PD and more than 140 molecular G6PD variants.[1,4]

G6PD deficiency is quite prevalent in many middle east and Mediterranean countries including Iraq.[2,5-8] Data regarding prevalence of G6PD deficiency are available from different parts of Iraq including Baghdad, Basrah and Duhok provinces[9-11]; however none are available from the northeastern province of Sulymania. Regarding molecular basis only one study has been published from Duhok.[11] The aim of the current study is to determine the prevalence of G6PD deficiency in random healthy males in the province, and its molecular basis among deficient individuals and to compare the results with those from Duhok and other surrounding populations.

METHODS

Sulymania is a large province in Northeastern Iraq that borders on Iran. It has a population of around 1.5 million consisting mainly of ethnic Kurds. This study was conducted between January 2007 and September 2007. The subjects enrolled were males attending the Central Laboratory (in Sulymania province – Iraq) for routine premarital investigations). The later is the only authorized laboratory in the province to provide the mandatory premarital investigations and receives around 30-40 couples per day.

The male partners of the first 10 couples attending the center were enrolled on two days of the week to ensure random sampling. Informed consent was taken form all enrollees and the study was approved by the appropriate ethical committees at the Sulymania and Duhok colleges of Medicine, Iraq.

A 4 ml sample was collected in K2-EDTA tubes from each enrollee. The sample was used first to screen for G6PD deficiency by fluorescent spot test,[12] using commercial kits (Randox Laboratories Ltd, Great Britain). Those who were found to be deficient, as well as an equivalent number of random non-deficient ones underwent further testing using a quantitative G6PD enzyme assay kit (Randox Laboratories Ltd, Great Britain) according to manufacturer instructions.

DNA was extracted by a phenol chloroform based method from specimens of patients determined to be G6PD deficient by the above procedures. The extracted DNA was then screened sequentially for four G6PD deficient mutations namely G6PD Mediterranean (563 C→T), G6PD Chatham (1003 G→A), G6PD Cosenza (1376 G→C), G6PD A- (202 G→A) using restriction fragments length polymorphism following amplification of DNA by Polymerase chain reaction (PCR/RFLP). The primers, restriction enzymes and procedural details used for each of these reactions were as detailed elsewhere.[11,13,14]

RESULTS

Specimens from a total of 838 male subjects were screened by the fluorescent spot test and fifty individuals (6.0%) were found to be G6PD deficient and were confirmed by quantitative enzyme assay. The mean G6PD enzyme levels in those who were deficient was 0.48 $\pm$ 0.17 U/g Hb, while it was 6.86 $\pm$ 0.93 in fifty random non-deficient subjects tested simultaneously. Only three of the G6PD deficient individuals reported a history of favism and none gave a family history of favism.

Molecular characterization of forty out the fifty G6PD deficient individuals, who had adequate samples or successful

DNA extraction, revealed that G6PD Mediterranean (563 C→T) was most common, being detected in 30/40 individuals (75%), G6PD Chatham (1003 G→A) was next with 4 patient (10%), while no cases with G6PD A-, or Cosenza were identified, leaving the remaining six cases uncharacterized. Two of the three individuals with history of favism were carriers of Mediterranean mutation, while one was a carrier of the Chatham mutation.

DISCUSSION

G6PD deficiency has been recognized as a common inherited hematological disorder in Iraqis since the 1970,[2] and a frequency of 6.0% as documented in this study is not unexpected and is comparable with a frequency of 6.3% found in a recent study from the capital Baghdad at the center of the country (6.1%)[9] and to prevalence rates reported from neighbouring Kurdish population of western Iran (5.3%).[15] However, it is lower than the prevalence of 10.9% from Kurdish population of Duhok and 15.3% reported from Basrah in Southern Iraq.[9-11] G6PD deficiency is common throughout the Eastern Mediterranean region, though its frequencies are variable and range between 2-65%.[5,9,10,15-18] The polymorphic frequency of G6PD in Sulymania and the rest of Iraq as well as the Eastern Mediterranean in general, has been linked to selective advantage offered by inheritance of the disorder in malarial endemic areas.[1] Sulymania, in particular, has been known to be highly endemic for malaria until the early 1990s.[19]

The Mediterranean variant (563 C→T) was found to be the most frequent variant in the Eastern Mediterranean countries, with figures ranging from 54% in Jordan to 91% in Kurds of Western Iran.[6,7,15,20-23] Our figures are rather less than those reported in Kurds from neighbouring western Iran, those of Duhok (87.8%) or from Kurdish Jews of 80-97%.[11,15,16] The wide distribution of the Mediterranean mutation within this region suggests that this mutation is quite ancient and may have spread by migrations that had taken place over millennia.[17]

The second most frequent variant detected by the current study is G6PD Chatham (1003, G→A) that was found in 10% of our deficient individuals. G6PD Chatham is recognized as one of the common variants worldwide,[15] and its frequency among other Eastern Mediterranean countries varies between 4 to 10%.[6,7,22,23] Our figures are quite similar to those reported among Kurds from Duhok and those from Iran, at 8.7 and 7.3% respectively.[11,15]

G6PD Cosenza (1376 G→C) has been reported in polymorphic frequency among Iranian Kurds.[15] Nevertheless, it was not identified in any case in the current study. Its absence maybe related to the smaller number of characterized cases. The African A- variant (202 G→A) was also not found. This is in contrast to some Arab Eastern Mediterranean countries where rates between 5.8-14.2% are reported. However, and similar to the current study, absence of this variant has also been described in reports among Kurds of Duhok and Iranian Kurds.[11,15] Absence of the variant in these areas is most likely related to fact that the Kurdish inhabited areas of Iraq and neighbouring Iran were, unlike Arabia, a much less likely destination of African gene flow.

In conclusion, this study has confirmed that G6PD deficiency is frequently encountered in Sulymania province and compares well with earlier reports from central Iraq and the neighbouring Iranian Kurdish population, though slightly less than reports from the Kurds of Duhok.[11] The study has shown that G6PD Mediterranean and Chatham constitute the large majority of the deficient variants, which is consistent with what we have demonstrated in our earlier study from Duhok.[11] Further studies on uncharacterized variants should be the next step and may uncover novel G6PD

deficient molecular variants.

ACKNOWLEDGMENT

The research was supported by a grant from University of Duhok, Iraq.

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پوختە

ڕێژا بەلاڤبوونێ و جورەکرنا گەردی یا کێماتیا ئەنزیمێ G6PD لپارێزگەها سلێمانیێ – باکورێ ڕۆژهەلاتێ عیراقێ

پێشەکی و ئارمانج: کێماتییا ئەنزیمێ G6PD مشەترین نەساخییا قنێتی یا خوینێ یە دناڤ عیراقیان دا. ڤەکولینان ڕێژا بەلاڤبوونا وێ ل چەند پارچێن عێراقێ دیارکرییە, بەلێ نە بەلاڤبوونا وێ و نە جورێن وێ بێن گەردی هاتینە ڤەکولینکرن لپارێزگەها سلێمانیێ – باکورێ ڕۆژهەلاتێ عیراقێ. ئارمانج ژ ڤەکولینێ دەستنیشانکرنا ڕێژا بەلاڤبوونێ و بنەمایێ گەردی یێ کێماتییا ئەنزیمێ G6PD لپارێزگەها سلێمانیێ.

ریکێن ڤەکولینێ: سەرجەمێ 838 کەسێن نێر بێن ساخلەم کورانە هاتنە وەرگرتن لپارێزگەها سلێمانیێ و لێنێرین کرن بو کێماتیا ئەنزیمێ G6PD بڕێکا تاقیکرنا فلورسنت سپوت. ئەگەر کێماتی هەبوو ئەنجام دهاتنە دوباتکرن بڕێکا تاقیکرنا چەندانی یا ئەنزیمی. ئەو کەسێن کیماتی هەی و نمونێ وان یێ باش DNA دهاتە ڤاڤارتن و شروڤەکرن بو چار جورێن گەردی بێن کێماتییێ, ئەوژی: G6PD Mediterranean، G6PD Chatham، G6PD A–و G6PD Cosenza.

ئەنجام: ێنجی 50 کەسان (6٪) کێماتییا G6PD لدەف دیاربوو. نمونێ چل ژوان یێ باش بوو بو شروڤەکرنێ ژبو هەر چار جورێن گـــەردی, و دیاربوو کو 30 ژوان (75٪) ژجـــورێ G6PD Mediterranean بـــوون و چارێن دی (10٪) ژجـــورێ G6PD Chatham و هیچ کەس ژ هەردوو جورێن دی نەبوون و 6 کەس نەهاتنە جورەکرن.

دەرئەنجام: ڤێ ڤەکولینێ ڕێژا بەلاڤبوونا کێماتییا ئەنزیمێ G6PD لپارێزگەها سلێمانیێ دیارکر کـو ئەو ژی 6٪ بوو کو بەری نوکە نەهاتبوو دیارکرن. هەروەسا دیـــاربوو کو جـــورێن G6PD Mediterranean و G6PD Chatham جورێن سەرەکی بێن کێماتیا G6PD نە ل ڤێ پارێزگەهێ.

الخلاصة

نسبة الانتشار و الأسس الوراثية لعوز نازعة الهيدروجين الكلوكوز 6 فسفات في السليمانية- العراق

خلفية واهداف البحث: ان عوز انزيم نازعة الهيدروجين الكلوكوز 6 فسفات هو من اكثر امراض الدم الوراثية انتشارا في العراقيين. أن العديد من الدراسات قد عنت بتحديد نسبة انتشاره في عدد من مناطق العراق، و لكن لم يسبق ان تم دراسة نسبة الأنتشار أو الضروب الوراثية في محافظة السليمانية- شمال شرق العراق. ان الدراسة الحالية هدفها ان تعالج هذه المسألة.

طرق البحث: تم التحري عن عوز نازعة الهيدروجين الكلوكوز 6 فوسفات في 838 من الاشخاص الأصحاء عشوائيا ومن محافظة السليمانية بأستعمال طريقة القطرة المتوهجة. و قد تم تأكيد النتائج لحالات العوز بواسطة حساب كمية الأنزيم. و قد تم عزل الدنا في العينات التي كانت كمية النماذج فيها كافية و من ثم التحري عن اربع من الضروب الواثية لهذا العوز وبطريقة تضاعف الدنا التسلسلي- طريقة تقييد الطول متعدد الأشكال. و شملت هذه الضروب البحر المتوسط ، جاتم ، كوسينزا و A السلبي بالتتابع.

النتائج: وجد أن 50 شخصا (6%) كان لديه عوز نازعة الهيدروجين الكلوكوز 6 فسفات. و قد كان لدى اربعين منهم نماذج كافية للتحري عن الضروب الوراثية الأربعة. و باجراء هذه الفحوص وجدنا ان 30 (75%) لديهم ضرب البحر المتوسط و 4 (10%) لديهم ضرب جاتم. و لم نجد أي حالة كوسينزا و A السلبي ، بينما بقيت 6 حالات مجهولة الضرب.

الاستنتاجات: وجدنا أن نسبة أنتشار العوز في السليمانية هي 6%، و هي منطقة لم تكن مدروسة سابقا". كما وجد أن ضربي البحر المتوسط و جاتم تشكل أغلبية الحالات في هذه المحافظة.

OCCUPATIONAL EXPOSURE TO LEAD IN DUHOK CITY, KURDISTAN REGION, IRAQ

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Submitted 6 Jun 2011; accepted 3 Dec 2011

ABSTRACT

Background and objectives Occupational exposures to lead remain a serious problem in many developed and developing countries. In developing countries, awareness of the public health impact of exposure to lead is growing but relatively few of those countries have introduced policies and regulations for significantly combating the problem. This study aimed to determine levels and nature of occupational exposure to lead in Duhok city, Kurdistan, Iraq.

Methods A cross – sectional study design was conducted on 520 individuals occupationally-exposed to lead to determine the degree of lead exposure.

The study population comprised of male workers with an age range of 10 to 64 years. The workers were chosen as a convenience sample so that nearly equal number of workers from each of the six occupations was included: gasoline power generators (n=120), industrial urban area (n=100), traffic policeman (n=100), petrol filing stations (n=100), petrol storage (n=50) and battery repairing workshop (n=50). Pre-tested questionnaire was designed to obtain information on age, residence, current occupation (period in year), and current history of cigarette smoking. Blood lead level was analyzed by flame atomic absorption spectrophotometer, Perkin Elmer Using a standardized procedure published by the company. Dust lead level was analyzed using the lead test kit (ABOTE × ENTERPRISES limited Ontario and a NOM).

Results The mean blood lead value among the sample was 14.5 ug/dl, with a standard error (0.46) and range (3.2 to 55.3). Of the 520 individuals tested, 54.4% subjects had blood lead level of 10 – 25 ug/dl, while 8.6% of these subjects had blood lead level 25 – 50 ug/dl and 1.2% had blood lead level> 50 ug/dl. The mean blood lead levels of the battery repairing workers (40.0 ug/dl) was significantly higher ($p< 0.001$ for all) compared to the gasoline power generator workers, petrol station, traffic policemen, petrol storage, and general work in industrial urban area who had mean blood lead levels of 11.5 ug/dl, 14.2 ug/dl, 8.4 ug/dl, and 13.8 ug/dl; respectively. A statistically-significant relationship was found between blood lead levels and age, amount of cigarettes smoked and dust lead level.

Conclusions The results of our study showed a high exposure level of lead occurs in occupationally -exposed workers with 9.8% prevalence of toxic blood lead of 25ug/dl.

Duhok Med J 2011;5(2): 76-85.

Key words: Blood lead, Occupational exposure, Lead toxicity

Lead, a ubiquitous and versatile metal, has been used since prehistoric times. It has become widely distributed and mobilized in the environment and human exposure to and uptake of this non-essential element have consequently

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increased.[1] At high levels of human exposure there is damage to almost all organs and organ systems, most importantly the central nervous system, kidneys and blood, culminating in death at excessive levels. At low levels, heme synthesis and other biochemical processes are affected, psychological and neurobehavioral functions are impaired, and there is a range of other effects.[2-4]

Lead poisoning associated with occupational exposure was first reported in 370 BC.[5] It became common among industrial workers in the 19th and early 20th centuries, when workers were exposed to lead in smelting, painting, plumbing, printing and many other industrial activities. In 1767, Franklin obtained a list of patients in La Charity´ Hospital in Paris who had been admitted because of symptoms, which, although not recognized then, were evidently those of lead poisoning. All the patients were engaged in occupations that exposed them to lead.[6-8] Much research over the last 30 years has demonstrated adverse health effects of moderately elevated blood lead levels, i.e. below 25ug/dl. The permissible exposure level in the ambient (air, water, soil, etc.) environment, as well as in the working environment, has therefore been progressively lowered .[9] Although the problems of overt lead poisoning have largely receded in developed countries, chronic exposure to low levels of lead is still a significant public health issue, particularly among some minorities and disadvantaged groups. Furthermore, both occupational and environmental exposures have remained a serious problem in many developing and industrializing countries.[10] However, considering that there are still many vehicles using leaded petrol, it is possible to find high lead levels in the general population in areas of heavy traffic. In addition, an important source of the metal is air contamination caused by the gasoline power generators and industrial activities which of large number distributed in most areas of Duhok city. The aim of this study was to determine the degree of lead exposure in a sample of occupationally –exposed workers in attempt to ascertain the nature of this exposure.

METHODS

The study was conducted in Duhok city which lies in the far north-west of Iraq and forms the center of western governorate in Iraqi Kurdistan Region. The city lies in the transitional area, between the wavy area and mountains.

Three areas in Duhok city were selected for data collection:

a- The down town where heavy traffic areas located in five streets were selected. These are the main streets in the city center and they cross the center from north to South and from west to East. There are large buildings, and many commercial and business centers located on both sides of those streets

b- City districts where high density areas of gasoline power generators and petrol filling stations are located. They were chosen in a way so that they represent different parts of Duhok city.

c- Industrial areas where two main industrial areas namely Baroshky and Malta were selected. Both are located within the border of Duhok municipality and included small factories, car repairing shops and other industrial related facilities.

A cross – sectional study design was conducted on 520 individuals occupationally - exposed to lead to determine the degree of lead exposure in the workers of Duhok city. Workers of six main occupations were assigned from different areas. They were all male with age range of 10 to 64 years. The workers were chosen as a convenient sample so that nearly equal number of workers from each of the six occupations was included in the sample. They were 120 gasoline power generator workers collected from those working in gasoline generators and distributed in all districts of the city, the

traffic policeman (n=100) collected from traffic policemen working in down town streets, the workers in petrol filling stations (n=100) colleted from petrol filling stations distributed in different parts of Duhok city, general industrial workers(n=100) engaged in different occupations such as car repairing, painting and other industrial related facilities, while the remainder were 50 petrol storage workers working in the main petrol storage bankers and 50 battery repairing workers mainly from battery shops located in the center of the city.

The study was conducted between 1 January and 31 December 2010 in the Department of Clinical Biochemistry and Community Medicine, College of Medicine, University of Duhok. The study protocol was approved by the Ethical Committee at the Directorate General of Health in Duhok governorate.

Pre-tested questionnaire was designed to obtain information on age, gender, residence, current occupation job period in year, current history of cigarette smoking.

The aim of the study was first explained and participant was then requested to give a blood sample. Five ml venous blood was withdrawn from each individual under study and transferred to EDTA – tube for the measurement of blood lead level. Since blood lead measurement is greatly affected by contamination all precautions to avoid any contamination were made, trace – element - free technique was used during the handling and analysis of blood samples. The samples were taken immediately to the Department of Clinical Biochemistry in Duhok Medical College. The blood lead was extracted by specific procedure and then samples were taken to the Department of Chemistry, College of Science, University of Duhok, for lead measurement.

Blood lead was analyzed by flame atomic absorption spectrophotometer (AAS), Perkin Elmer using a standardized procedure published by the company. Radiation source absorbance was measured at a wavelength of 283nm, using a band pass of 0.7 nm. Briefly EDTA – blood precipitated with 20 % trichloroaceticacid (TCA) solution. The supernatant solution is aspirated directly in the AAS; the samples were run in batches using standard lead solution of 10, 25 and 50 ug / dl to correct the sensitivity of the instrument. Reagent blank prepared by mixing equal volume of 20 % TCA with deionized water. The blank gave a reading of 1 ug/dl and this value was subtracted from the reading of the samples examined. A pooled normal blood was run with every batch and gave a reading of 12 ug/ dl. Serial replication of aliquots from a pooled blood sample and an internal control standard were used to cheek the precision and accuracy of the analytical method.

The coefficient of variation (CV) for lead in a pooled blood was 3.5 % (n = 30). Values for the internal control standards (CRDL standard 2 solutions; Radian Corp TX USA) intercalculated between every 10 samples in the rack of samples with each new analysis batch. Samples which did not differ by more than 2 % of the standard value were considered acceptable.[11] All samples were analyzed in triplicate and results referred to the standard curve made previously. The atomic absorption spectrophotometer was adjusted according to the Perkin Elmer Analyst instructions.[12]

Roadside samples were collected for determination of dust lead level from the areas of selected occupational samples. The dust samples were taken in combination with blood samples. Dust lead level was measured by using the lead test kit purchased for this purpose (ABOTE × ENTERPRISES limited Ontario and a NOM:T website www.leadinspection.com).

This lead test kit utilizes patented leach method for testing; this method gives semi – quantitative results which indicate the approximate lead release in sample. The dust samples were used to assess lead

from renovation areas following the instructions for the technique described in the kit. After the comparison of the resultant color produced, the concentration of lead is shown into part per million (ppm).

Lead exposure has been identified on the determination of blood lead and dust lead levels. The highest value proposed for lead exposure in children is > 10 ug/dl and > 25 ug/dl in adults being the most conservative was selected for this study as the cutoff for high blood lead concentration.[10] Dust lead level < 5 ppm was considered as a cutoff value for low level of lead exposure whereas a level of > 25 ppm indicated high level of lead exposure to check environmental lead exposure.

Data were translated into a computerized database structure. An expert statistical advice was sought for. Statistical analyses were computer assisted using SPSS version 13 (Statistical Package for Social Sciences). Frequency distribution for selected variables was done first. ANOVA test was used to test the statistical significance of difference in mean between more than 2 groups. The chi-squire test was used to assess the statistical significance of association between 2 categorical variables.

RESULTS

Mean blood lead value in the sample was 14.5ug/dl with a standard deviation 6.2 ug/dl and a maximum 55.3 ug/dl (Table 1). The mean blood lead levels of the battery repairing workers (40.0 ug/dl) was significantly higher (p< 0.001 for all) compared to the gasoline power generator workers, petrol station, traffic policemen, petrol storage, and general industrial workers who had mean blood lead levels of 11.5 ug/dl, 14.2 ug/dl, 8.4 ug/dl, and 13.8 ug/dl; respectively. Considering only the occupational hazard, there was 54.4% of the occupational workers had blood lead level 10 – 25 ug/dl, while 8.6% of these workers had blood lead level 25 – 50 ug/dl and 1.2% had blood lead level >50 ug/dl (Table 2). No differences were observed in blood lead levels among the different periods of work in current job (i.e. 8.6% of workers with duration of work in current job <10years had blood lead level >25 ug/dl compared to 12.5% of workers with duration of work in current job >10 years at the same blood lead, p=0.18). In the sample (Table 3), blood lead levels in older age groups (25.6± 15.5 ug/dl) were significantly differ from those of younger age group (5.4+1.7 ug/dl), (p<0.001). Blood lead levels showed a linear relationship with age i.e. the older the individual, the higher the blood lead values. Regression coefficient value r= 0.654 and p value <0.001 (Figure 1).

Table 4 shows blood lead levels according to the amount of cigarettes smoked (average/day); which were higher in cigarettes smoking group. The difference was statically significance (p <0.001).

The mean blood levels were increased with increasing dust lead levels in the working area, i.e. the overexposure to lead, the higher the blood lead values (Table 5). Generally, dust lead levels of various working area were in the range of 10-50 ppm (95.0%). Table 6 shows the median dust lead concentrations of the occupational areas. Traffic Policemen areas were ranked the lowest by having average dust lead level of 10-25 ppm (69%).

Table1. Blood lead levels according to type of occupation

Type of occupation	Blood lead concentration (ug/dl)					
	n	Mean	SD	SE	Range	p (ANOVA trend)
Gasoline power generators	120	11.5	4.3	0.39	3.2-19.2	<0.001
Petrol station	100	14.2	3.5	0.35	5.4-19.9	
Traffic policemen	100	8.4	2.2	0.22	4.8-14.8	
Battery repairing	50	40.0	9.3	1.31	18.4-55.3	
Petrol storage	50	10.1	3.0	0.43	7.2-23.7	
General industrial work	100	13.8	4.8	0.48	8.0-27.1	
Total	520	14.5	6.2	0.43	3.2-55.3	

Table 2. Distributions of the sample by blood lead level range

	Blood lead range ug/dl				
	< 5.0 n (%)	5.0 – 10.0 n (%)	>10.0 – 25 n (%)	>25 – 50 n (%)	50 + n (%)
Gasoline power generators	8 (6.7)	35 (29.1)	77 (64.2)	-	-
Petrol station	-	12 (12.0)	88 (88.0)	-	-
Traffic policemen	10 (10.0)	71 (71.0)	19 (19.0)	-	-
Battery repairing	-	-	6 (12.0)	38 (76.0)	6 (12.0)
Petrol storage	-	30 (60.0)	20 (40.0)	-	-
General Industrial work area	-	20 (20.0)	73 (73.0)	7 (7.0)	-
Total	18 (3.5)	168 (32.3)	283 (54.4)	45 (8.6)	6 (1.2)

Table 3. Blood lead levels according to age of occupational sample (n=520)

Age (years)	Blood lead concentration (ug/dl)					
	n	Mean	SD	SE	Range	p (ANOVA trend)
10-16	18	5.4	1.7	0.39	(3.2 - 8.3)	< 0.001
17-29	269	11.1	5.4	0.33	(3.7 - 34.8)	
30-39	158	15.9	7.7	0.61	(8 - 43.6)	
40+	75	25.6	15.5	1.79	(10 - 55.3)	
Total	520	14.5	6.2	0.43	(3.2 - 55.3)	

Table 4. Lead levels according to cigarettes smoking (n=520)

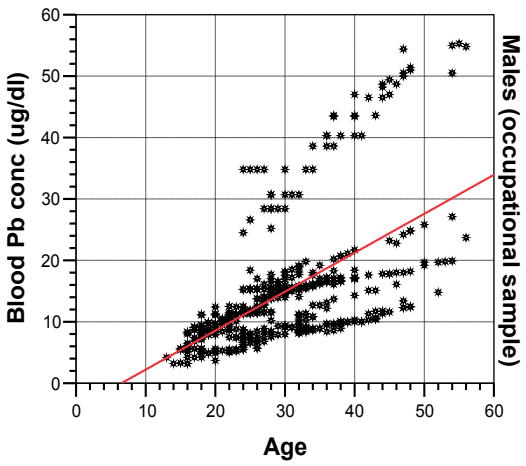
Smoking categories (Average/day)	Blood lead concentration (ug/dl)					
	n	Mean	SD	SE	Range	p (ANOVA trend)
Never smoked	203	8.3	5.4	0.24	3.2-40.3	< 0.001
Half a pack or less <10)	97	12.7	2.7	0.27	3.7-17.0	
One pack (20)	109	16.7	7.7	0.36	3.8-50.5	
> one pack	111	25.3	9.3	1.81	5.2-55.3	

Table 5. Blood lead levels according to the average dust lead levels in the working area

Dust lead level (ppm)	Blood lead concentration (ug/dl)					
	n	Mean	SD	SE	Range	p (ANOVA trend)
1-5	13	4.2	0.6	0.04	(3.2 - 7.9)	< 0.001
10-25	178	7.4	1.8	0.08	(4.2 - 24.5)	
>25-50	317	15.1	7.2	0.31	(8.4 - 49.4)	
>50	12	45.9	12.2	3.51	(25.2 - 55.3)	

Table 6. The median dust lead concentration by selected independent variables

Occupational hazards	Dust Pb average concentration (ug/dl)							
	(1-5) n (%)	(5.1-10) n (%)	(10.1-25) n (%)	(25.1-50) n (%)	>50 n (%)	Total n (%)	Median	p (Kruskal-Wallis)
Gasoline power generators	0 (0)	8 (6.7)	35 (29.2)	77 (64.2)	0 (0)	120 (100)	(25.1-50)	< 0.001
Petrol station	0 (0)	0 (0)	18 (18)	82 (82)	0 (0)	100 (100)	(25.1-50)	
Traffic policemen	0 (0)	5 (5)	69 (69)	26 (26)	0 (0)	100 (100)	(10.1-25)	
Lead battery	0 (0)	0 (0)	2 (4)	39 (78)	9 (18)	50 (100)	(25.1-50)	
Petrol storage	0 (0)	0 (0)	30 (60)	20 (40)	0 (0)	50 (100)	(10.1-25)	
General industrial work	0 (0)	0 (0)	24 (24)	73 (73)	3 (3)	100 (100)	(25.1-50)	
Total	0(0)	13(2.5)	178(34.2)	317(60.9)	12(2.3)			



R = 0.654; p < 0.001

Figure 1. Scatter diagram with fitted regression line showing the linear correlation of blood lead concentration with age in study group

DISCUSSION

It has been reported that the main noxious effects of lead are produced at high exposure levels as occurs in occupationally-exposed workers.[13] In urban setting, the main source of lead to which the general population is exposed is the combustion of leaded petrol, but other possible source, such as industrial contamination can be considered in areas with less air contamination For many reasons, the workers of Duhok city have a probable risk of over-exposure to the metal. However, considering that there are large numbers of vehicles and electrical generators coinciding with the widespread use of leaded petrol, it is possible to find high lead levels among general population in areas of heavy traffic and crowd. Also, the geographical location of the city between two mountains and location of general industrial workshops within the border of Duhok municipality may suggest high levels of exposure. Hence, it is essential to know the degree of exposure of the study sample so that the necessary control measure can be established. To our knowledge, this is the first study to investigate the sate of the occupationally-exposed workers regarding lead exposure in Duhok city.

Notwithstanding, the results of our study showed mean blood lead levels of the study sample of 14.5 ug/dl, which are far below the currently accepted toxicity threshold 25 ug/dl. Other studies conducted in different parts of Iraq.[13-16] obtained higher results with mean blood lead levels of around 23.7ug/dl. These values were markedly higher than ours, probably due to the origin of their sample which was taken mainly from battery workers. In this study, there were 64.2% of workers who had the blood lead higher than10 ug/dl. Among this group, 51(9.8%) workers had higher blood lead level than 25 ug/dl, which most of them were battery workers. Our results, in comparison, reflect a low blood lead levels; for example, none of the policemen had blood lead level more than 25 ug/dl and the mean was slightly lower (8.4 ug/dl) compare to those obtained in the previous studies in Iraq (13.7 ug/dl),[17] which appears to indicate that the measures taken to reduce the quantity of lead in petrol have contributed to the progressive decrease in atmospheric lead levels. This finding confirmed by the low median dust lead concentration in the traffic policemen areas. However, our results overall show higher values in workers of gasoline generators, petrol station, petrol storage and general industrial work, although, the values still within the acceptable range (3.2-27.1 ug/dl).

With respect to blood lead-related factors, our overall results show higher values in workers with the heavy lead dust working area. Other studies concur with this observation of higher values in working areas with greater occupational contamination by the metal .[18] Results obtained for intoxication prevalence are similar, since a greater prevalence was observed in workers in the area with dust lead level of 25 ppm (60.9%). A statistically-significant relationship is found, however, between blood lead and age; higher blood lead levels are observed in older workers who have been exposed to higher lead contamination levels. We found a tendency towards increased blood lead values with the increase in average cigarettes smoking. The main route of lead absorption may be through inhalation, however, inadequate hand- and face-washing and unrestricted smoking and eating at the workplace may result in high lead exposure.

In conclusion, our study has demonstrated elevated blood lead levels in battery repairing workers for whom the safety control measures should be apply first. Whereas in the reminder of workers, this study indicates that lead exposure does not constitute a great health problem if occupationally-exposed workers considered, since levels found are below

those deemed toxic and the prevalence of intoxication is similar to that reported in other studies.

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پوختە

بەرهنگاربونا رصاصی ژ کاری لناڤ باژێرێ دهوکێ

پێشەکی و ئارمانج: بەرهنگاربون بو رصاصی هێشتا ئاریشەکا مەترسیدارە ل سەر گەلەك ولاتێن پێشکەفتی و وەلاتێن پاشکەفتی وناڤەندی گەلەك پاشماییێت سەرەکی بێن خراب هەنە ژ ئەگەرێ زێدەبونا ریژا رصاصی لناف خوینێ دا لنك کرێکاران ل جهێن کاری کار دکەن.

ریکێن ڤەکولینێ: ئەڤ ڤەکولینە لسەر کرێکاران هاتیە کرن کو سەرەجهێ وان دبیتە 520 بەشداربویا ودابەش کرینە ل سەر شەش گروپێن کرێکارێن موەلیدا وکرێکارێن پانزینخانا وپولیسێن هاتن و چوونێ وکرێکارێن گهورین وفروتنا پیلەکێن ترومبێلا وکرێکارێن عمبارێن پترولێ وکرێکارێن پێشەسازی ل دهوکێ. ئەو شلوڤەکرنێن ل سەر خوینێ هاتینە کرن بخوڤە دگریت پێوەرێن ریژا رصاصی وئەکتیڤیا ئەنزیمێ ئەماینولیڤولینك ئەسید دیهایدرێز وهندەك شلوڤەکرنێن دی وەك ریژا رصاصی لناف هروباییێت زەپوشێ وهندەك پێوەرێت دی وەك ژی وجگەرەکێشانێ.

ئەنجام: د ئەنجاماندا دیاربوو کو ریژا رصاصی لناڤ خوینێ یا بەرزە لنك کرێکارێن شولێ گهورین وفروتنا پیلەکێن ترومبێلا دکەن براوردی دگەل کرێکارێن دی.

دەرئەنجام: دڤێت رێکێن ساخلەمیا گشتی بێتە وەرگرتن دا کو ریژا رصاصی زێدەنەبیت لدەف هەمی کرێکاران ویا دیار بو کو بەرزبوونا ریژا رصاصی دناڤ خوینێ دا ژبەر بەرهنگاربوونێ ل دەف کرێکاران وریژەیا 9.8 ٪ گەهشتە پلەیا ژەهربوونێ ئەوا کوپ تر ژ 25 مایکروکرام/ دسلیتر.

الخلاصة

التعرض المهني للرصاص في مدينة دهوك

خلفية واهداف البحث: التعرض للرصاص يمثل مشكلة خطيرة في العديد من البلدان المتقدمة والبلدان النامية وان الاثار الضارة للرصاص وبتراكيز عالية من التعرض للرصاص تحدث عند العمال المعرضين مهنياً في مواقع العمل.

طرق البحث: شملت الدراسة 520 مشاركاً مقسمين الى ستة مجاميع وهم عمال المولدات وعمال محطات التعبئة وشرطة المرور وعمال تبديل وشحن بطاريات السيارات وعمال مخازن المشتقات النفطية وعمال المنطقة الصناعية في دهوك وان التحاليل التي اجريت على الدم تتضمن قياس مستوى تركيز الرصاص وفعالية انزيم امايونوليفولينك اسيد ديهايدرتيز ومحاليل اخرى لقياس مستوى الرصاص في الغبار والهواء. وتم الاخذ بنظر الاعتبار العمر والتدخين.

النتائج: أظهرت النتائج ارتفاع معدل مستوى تركيز الرصاص في الدم عند العمال الذين يتعرضون بصورة مباشرة للرصاص وخاصة الذين يعملون في محلات تبديل وشحن وتصليح بطاريات السيارات مقارنة مع بقية مجاميع العمال.

الاستنتاجات: يجب اتخاذ تدابير الرقابة والسلامة العامة للحد من ارتفاع معدلات الرصاص لدى العمال لأنه تم ملاحظة ارتفاع نسبة معدل الرصاص في الدم نتيجة تعرض العمال مهنياً له وأن نسبة 9.8 % بلغت مرحلة التسمم والتي هي أكثر 25 مايكروكرام/دسليتر.

THE ROLE OF ULTRASOUND VERSUS PHYSICAL EXAMINATION IN THE MANAGEMENT OF DEVELOPMENTAL DYSPLASIA OF THE HIP DURING THE FIRST SIX MONTHS OF LIFE

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Submitted 16 Jun 2011; accepted 3 Dec 2011

ABSTRACT

Background and objectives The hip joint is largely cartilaginous during the first six months of life. Therefore; ultrasound has been increasingly used for the initial diagnosis of developmental dysplasia of the hip. Because the hip joint maturation is fastest during the first three months of life, early intervention provides a better prognosis. Hence, there is an important need for initial screening and early management of developmental dysplasia of the hip. The aim is to assess the role of ultrasound versus physical examination in the initial diagnosis of developmental dysplasia of the hip at the age of 0-6 weeks of life. As well as, to evaluate their roles in subsequent follow-up after a period of monitoring and/or intervention until the age of 6 months.

Methods 150 infants (5 days to 6 weeks of age; mean age was 4 weeks) underwent physical and ultrasound examination for developmental dysplasia of the hip. The hips were classified according to the Graf technique and were followed-up prospectively by ultrasound and physical examination up to the age of 6 months to monitor the response to treatment.

Results The mean age of babies at first examination was 4 weeks. Only 38.5% of developmental dysplasia of the hip cases on ultrasound were found to have abnormal physical examination. There was a statistically significant association between developmental dysplasia of the hip and the presence of risk factors (p value < 0.05). During 6 months of follow up, 30 cases of developmental dysplasia of the hip were diagnosed. Healing of the joints with treatment occurred for all developmental dysplasia of the hip cases but in different durations. No significant complications of treatment were reported by the age of 6 months.

Conclusions Babies with normal hips on examination can have developmental dysplasia of the hip on ultrasound. On the other hand, babies with normal hips on ultrasound scan can show clinical instability. Ultrasound is a better and most practical screening tool available for the initial diagnosis of developmental dysplasia of the hip. Furthermore, it can be successfully used for follow-up in order to show the response to treatment.

Duhok Med J 2011;5(2): 86-96.

Key words: Ultrasound, Developmental dysplasia of the hip, Initial screening, Management, Physical examination, Graf technique

Developmental dysplasia of the hip (DDH) describes a spectrum of abnormalities including acetabular dysplasia without displacement, subluxation and dislocation.[1] Normal acetabular and femoral head development depends on the concentrically placed femoral head. On the other hand, it has been found that the hip joint maturation is greatest during the first 3 months of life.[2] Therefore; the early diagnosis and intervention are important to identify at risk babies who are at critical age for hip joint maturation and to improve the treatment outcome. In certain regions in the world, particularly in places with high incidence of DDH, there is a high chance of missing cases of DDH.[3-5] While in countries with the introduction of screening program for DDH, the

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incidence of late diagnosis have been dramatically reduced.[6,7] Several methods have been used for the early detection of DDH in research and clinical practice. In a meta-analysis by Lehman et al, the incidence of DDH was found to be 11.5 per 1000 by physical screening and 25 per 1000 by ultrasound (US) examination.[8] This difference in DDH detection in the early period of life may be due to a number of reasons. Mark et al detected hip abnormality by US that was considered normal by physical examinations and in hips without risk factors.[9] These findings were supported by a different study which suggested that some patients with DDH do not have signs of clinical instability.[10] Furthermore, ultra-sonographically diagnosed acetabular dysplasia may be normal on physical examination.[11] On the other hand, the clinical screening by Ortolani and Barlow tests might damage the acetabulum, labrum and femoral head.[12] Therefore, such studies suggest the superiority of US over physical examination in detecting DDH.

During early periods of life, X-ray is largely replaced by US for the diagnosis of DDH due to two main reasons.[13-16] Firstly, the hip joint is largely cartilaginous at that age period and therefore US will be more informative. Secondly, US is not associated with risks of X-ray exposure. However, with progressive development of the femoral head ossification center, the US becomes less useful and follow-up can be continued by X-ray after 6 months of life.[2,15,16]

The most commonly used method of US in the diagnosis of DDH is the Graf technique.[2] This technique reduced the age of treatment in babies with DDH from an average of 8 months to an average of the first few weeks of life.[16] Therefore, Graf technique has the advantage of early detection and management. Nevertheless, this technique is not free from drawbacks. Dias et al found that the reproducibility of the measurements using the Graf technique is not very great.[17] Moreover, this technique involves only static morphological examination and it does not consider the presence of hip instability and ligament laxity.[16] However, these two drawbacks of Graf technique do not affect the overall classification and hence this technique can be used successfully for the early detection and subsequent management of DDH.[16] Graf classified DDH according to the morphological examination of the hip joint by US, (Figure 1).[2,15] He classified the hip joint as mature (type I), immature (type II), dislocated (type III) and highly dislocated (type IV) (Table 1). Some authors suggested that the average time for maturation for each type of Graf can be predicted.[18] Healing for Graf type IIa, Graf type IIb and Graf type D will require 3 weeks, 5 weeks and 8 weeks, respectively. While longer healing time will be required for type IIIa (14 weeks), type IIIb (18 weeks) and type IV (24 weeks).

Graf has suggested a protocol for management of DDH according to the type at initial US examination.[2] Hips that are diagnosed as type I at 3-6 weeks of life can be safely discharged. 95% of those with type IIa will be recovered spontaneously and therefore only need to be monitored without any sort of treatment.[16] The remaining 5% who do not recover at 6 weeks follow up should be fitted with a Pavlik harness. Whereas, stable dysplastic hips (IIb and stable IIc) should be put in Pavlik harness until they become type I. Unstable type IIc should pass through both retention and maturation phase. The plaster cast in human position can be used to serve retention phase. The decentered hips (type D, III and IV) require reduction before retention and maturation.

The aim of this study was to assess the role of US versus physical examination in the initial screening of DDH hip at the age of 0-6 weeks of life. Moreover, their roles in the subsequent follow-up and management until the age of 6 months have been evaluated.

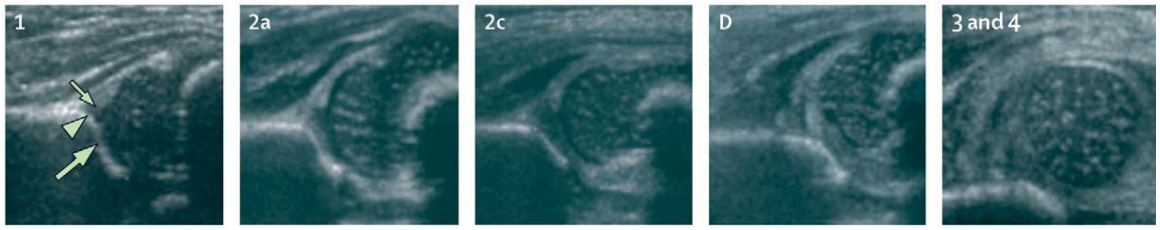


Figure 1. Types of DDH according to Graf classification. Pictures were taken from the work of Dezateux C and Rosendahl K[15]

Table 1. Hip types according to Graf classification[2]

Graf type	Alpha angle/Bony roof	Beta angle/Cartilaginous roof	Age
Type I	≥ 60°	<55°	any age
Type IIa	50–59°	covers the femoral head	0 to 12 weeks
Type IIb	50–59°	covers the femoral head	>12 weeks
Type IIc	43–49°	<77 (still covers the femoral head)	any age
Type D	43–49°	>77 (displaced)	any age
Type III	<43°	pressed upwards	any age
Type IV	<43°	pressed downwards	any age

METHODS

This is a prospective comparative cohort study of 150 neonates aged between 5 days to 6 weeks at the time of first US examination. The study covered the period between 01/05/2010 to 28/02/2011. Each subject was followed monthly for up to six months of life or until the result of the US had become normal.

This study targeted infants presented to Helena Health Center for Disabled Children/Erbil-Iraq for assessment of DDH. The 3 main origins of referrals were: Erbil's Maternity and Pediatric Hospital, Raperin Pediatric Hospital and primary health centers in Erbil. Infants presented by concerned parents were also included in the study. The inclusion criteria for subject selection and recruitment were infants between 0 to 6 weeks of age. Exclusion criteria were infants with teratological DDH and/or Infants with cerebral palsy.

Physical examination (Ortolani and Barlow tests) were performed on all babies at the time of initial presentation. The results of these two tests were classified as positive and negative. Follow-up was done by physical examination including examination for late features: limited abduction, asymmetrical skin creases and shortening (Galeazzi's sign). The physical examination was performed before US, in order to blind the examiners to the result of US.

The ultrasound machine (ESAOTE Pie Medical) was used, which is the device available at Helena Health Centre. We used the standard hip US probe that is linear transducer with a frequency of 7.5 MHz. The US examination was performed by an orthopedic surgeon who was certified by Professor Graf (Figure 2).

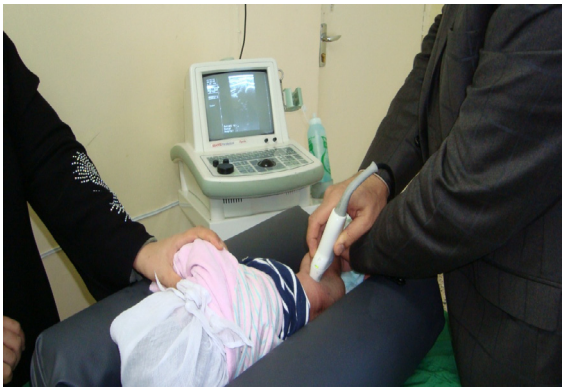


Figure 2. Graf technique of Hip examination by US. The picture shows a baby in a cradle with correct placement of the probe over hip joint

Alpha angle is representing an angle between the base line (a line that is tangential to os ileum at the top of the cartilaginous roof) and the bony roof line (a line from the distal end of os ileum tangential to the bony roof). Beta angle is representing an angle between the base line and the cartilaginous roof line (a line that is drawn from the bony rim through the middle of labrum) (Figure 3).

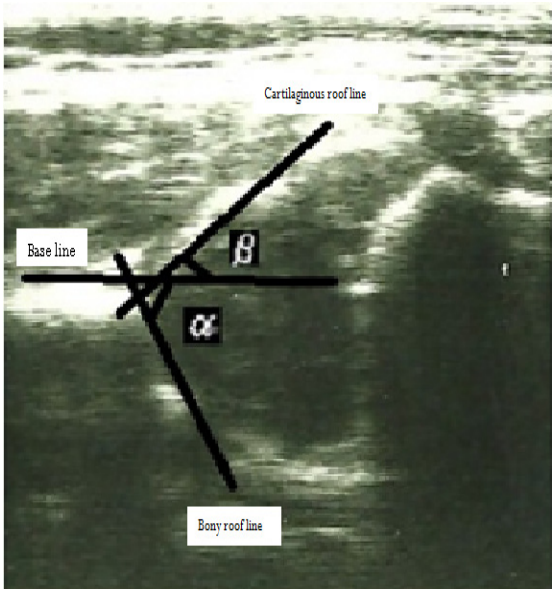


Figure 3. Alpha angle is representing the bony roof of acetabulum and Beta angle is representing the cartilaginous roof of acetabulum

The operators scored individual babies for positivity and then severity of DDH based on Graf scoring (Alpha and Beta angles). Those who were diagnosed as type I were discharged but re-examined by US at age of 3 months. Those who were diagnosed as type IIa were followed up to three months of age. If their hips were still immature at that age, they were classified as type IIb. Those who changed to type IIb and those who diagnosed initially as Graf type IIc, type D, type III and type IV were defined as DDH and they received treatment according to the principles of management by Graf.

A pre designed proforma was used to collect basic biographical data as well as the result of the Graf scoring.

The splint was checked at each visit to make sure that it was properly applied and the child was properly cleaned. The compliance of the parents was also checked. Prompt evaluation was performed to exclude complications including recurrence, avascular necrosis and stiffness. X-ray was performed at 6 months of age for those who received treatment to exclude recurrence and avascular necrosis. Delay in appearance of bony nucleus on US and/or X-ray or increased density of bony nucleus on x-ray were considered as avascular necrosis.

Microsoft excel 2007 was used for statistical tests. Results were presented as number and percentage. P value was identified by using chi-square test. P value of less than 0.05 was regarded as statistically significant.

RESULTS

155 babies were examined for DDH by US. 5 of them were dropped out of the study. Therefore, 150 babies (300 hips) were included in the statistical tests. The result of the initial US examination according to the Graf is shown in table 2. The mean age of the babies at first US was 4 weeks (range: 5 days to 6 weeks). 59.2% (N 89) were female versus 40.8% (N 61) were male (Table 3 and 4). Of those who were diagnosed as DDH at initial US examination, 16 were left sided and 2 were right sided (4 babies had bilateral DDH).

Table 2. Graf types at the initial US examination

Graf classification	Number of hips (%)	Left hip (%)	Right hip (%)
Type I	232 (77)	101 (67.3)	131 (87.3)
Type IIa	42 (14)	29 (19.3)	13 (8.5)
Type IIc	18 (6)	15 (10)	3 (2)
Type D	2 (0.3)	1 (0.6)	1 (0.6)
Type III	6 (2)	4 (2.6)	2 (1.3)
Type IV	0 (0)	0 (0)	0 (0)
Total (%)	300 (100)	150 (100)	150 (100)

Table 2. Initial physical and US examination in female babies

Physical hip examination	Graf type						
	I No. (%)	IIa No. (%)	IIc No. (%)	D No. (%)	III No. (%)	IV No. (%)	Number of hips (%)
Normal	122 (95)	26 (87)	12 (81)	0	1 (25)	0	161 (90)
Abnormal	6 (5)	4 (13)	2 (19)	2 (100)	3 (75)	0	17 (10)
Number of hips (%)	128 (72)	30 (17)	14 (8)	2 (1)	4 (2)	0	178 (100)

Table 4. Initial physical and US examination in male babies

Hip physical examination	Graf type						
	I No. (%)	IIa No. (%)	IIc No. (%)	D No. (%)	III No. (%)	IV No. (%)	Number of hips (%)
Normal	100 (96)	10 (85)	2 (50)	0	1(50)	0	113 (93)
Abnormal	4 (4)	2 (15)	2 (50)	0	1 (50)	0	9 (7)
Number of hips (%)	104 (85)	12 (10)	4 (3)	0	2 (2)	0	122 (100)

About 10% (4 hips) of those who were diagnosed as type IIa at initial examination were changed to type IIb at 3 months of age. The frequency of DDH among all hips was 30 (10%). Among the females, there were 24 (13.5%) hips that diagnosed as DDH versus 6 (5%) hips among the boys. The total number of infants who were diagnosed as DDH was 26 (22 unilateral; 4 bilateral).

Positivity status of DDH according to physical examination versus US examination at time of initial screening is shown in table 5. Of the 26 hips which were abnormal on physical examination, 38% were also found to be abnormal by US. On the other hand, in 274 clinically normal hips, 16 (6%) hips were turned to be abnormal on US. There was a statistically significant difference between the positivity of physical examination and US for DDH ($p < 0.05$).

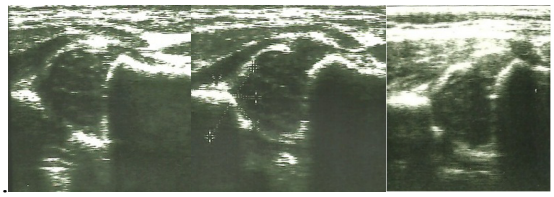
As far as the follow-up is concerned, all of the hips diagnosed as Graf type I by US remained Graf type I at three months of age. 4 of Graf type IIa had changed to Graf type IIb by three months of age. The rest of Graf type IIa hips changed to Graf type I spontaneously by three months of age. Those who were diagnosed as DDH (Graf type IIb, IIc, D and III) were treated and changed to normal hips as shown on the subsequent US during the first 6 months of age (Figure 4).

Table 5. DDH according to physical examination versus US examination at 0 to 6 weeks of age

Hip physical examination	US examination		Total
	Mature & physiological No. (%)	Pathological No. (%)	
Normal	258 (94)	16 (6)	274
Abnormal	16 (61.5)	10 (38.5)	26
Total	274 (91.3)	26 (8.7)	300

The positive Ortolani and the Barlow tests became negative by the second month of life. None of the babies with DDH had abnormalities on physical examination for late features at follow-up.

The frequency of risk factors in babies with DDH is shown in table 6. There was a statistically significant association between DDH and the presence of risk factors ($p < 0.05$).



A B C

Figure 4. A newborn baby with Graf type III at 3 weeks of age (A) treated by hip spica and then Pavlik harness. Follow-up at 3 months (B) and 4 months (C) of age demonstrated significant improvement of alpha angle and femoral head coverage

Table 6. The association between risk factors and DDH

Risk factors	Infants with DDH		Total
	Yes	No	
Positive	22	68	89
Negative	4	56	61
Total	26	124	150

Further analysis was performed to determine the average time of hip joint healing post treatment. The healing time for hip joint increased with the increase in the grades of Graf types (Table 7).

Table 3. Average time of hip joint healing according Graf types

Graf Types	Average time of healing in weeks
Graf type IIb	6 weeks
Graf type IIc	8 weeks
Graf type D	10 weeks
Graf type III	16 weeks

Only two babies who wore the Pavlik harness developed skin rashes. At 6 months of age, there was no evidence of avascular necrosis of the femoral epiphysis, recurrence or hip joint stiffness (Figure 5).

DISCUSSION

The earlier the diagnosis and the management of DDH, the better the result will be.[2,7,16] Two most commonly used approaches for early diagnosis of DDH in literature are physical examination and US.[1,2,14,19] In a sonographic approach to early diagnosis and treatment of DDH, it has been found that only US can permit early diagnosis of acetabular dysplasia.[20] In this study, only 38.5 % of hips diagnosed as abnormal on examination were also found to be abnormal on US. The rest of DDH (61.5 %) by US were found to have normal hips by physical examination. Therefore, patients with DDH might have normal physical examination. This is consistent with the literature as it shows that the incidence of DDH by US is higher than incidence of DDH by physical examination.[8] This discrepancy between US and physical examination was also found among patients with Graf type III and type IV.[13] About 6 % of mature and physiological hips by US were found to have clinical instability at 4 weeks of life (mean age). The same finding was evident in other studies.[10,14] Barlow (1962) suggested that about 88 % of clinically unstable hips will normalize by 8 weeks.[21] Furthermore, the inter-observer reliability for the physical examination is poor.[22] Moreover, some tests for clinical instability such as Barlow test can dislocate the joint in an otherwise normal baby.[7,23] The mentioned disadvantages of physical examination support even further the early use of US.

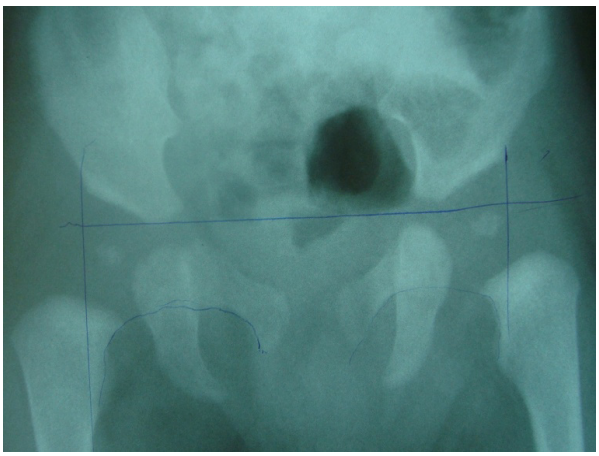


Figure 5. Post-treatment x-ray of the same baby at 6 months of age (who diagnosed as type III left DDH by US at 3 weeks of age). There is no evidence of avascular necrosis or recurrence

It has been reported that newborn babies may have normal US examination at birth but may develop DDH later by the age of three months.[14] Dogruel et al. found that 15 out of 838 Graf type IIa babies had changed to Graf type IIb at the age of three months and they required treatment.[14] Similarly, in our study, 4 babies with Graf type IIa had failed to become mature and they were classified as Graf type IIb. Therefore, at least two US examinations is recommended for babies with Graf type IIa (initial US at 4 weeks; second US at 3 months).[24]

The Ortolani and Barlow tests became negative by the second month of age even in the patients with DDH. It has been reported that the reliability of these 2 tests will be poor after the first few months of life.[16] Therefore, the mentioned tests cannot be used for follow-up and monitoring treatment. Moreover, in this study, the babies with DDH did not show late signs of the disease. Limited abduction, asymmetrical skin creases and shortening are considered to be late features in untreated DDH. [1] Because, the intervention had started early in this study, the patients did not show the late features. Furthermore, the late features are not reliable for follow-up in the first 6 months of life[16,19]; asymmetrical skin creases may be present in babies with normal hips, specificity and sensitivity of limited abduction is 54% and 69%, respectively. Similarly, Galeazzi's sign may not detect subtle DDH and is negative in babies with bilateral DDH.[13] However, these late features may be more reliable for missed cases of DDH after 6 months of life.

On the other hand, we followed-up babies with DDH by regular US. All of these babies were treated successfully and confirmed to be normalized at the age of 6 months by US and X-ray.

It has been found that babies with risk factors are more likely to have DDH than those without any risk factors.[14] There was significant association between the presence of DDH and risk factors in this study. On the other hand, Lewis et al. recommended US examination for all newborn babies as they found cases of DDH without risk factors.[24] But as mentioned earlier, the problem with universal screening is that US may diagnose a large number of newborn babies with immature hips that do not require treatment and resolve spontaneously as well as issues related to cost and resource implications. Consequently, there is an ongoing debate about the rational and the utility of screening for all newborn babies. In certain countries, such as the United Kingdom, US is only used when there are risk factors or physical abnormalities suggestive of DDH. However, US screening is more widespread in countries with higher incidence of DDH such as in German-speaking countries.[16]

Those diagnosed as Graf type IIb and Graf type IIc were put in the Pavlik harness until the heads were healed (average: 6 weeks for Graf IIb; 8 weeks for Graf IIc). The fast hip joint maturation during the first 3 months of life can shorten the period of treatment.[2] Therefore, early intervention and treatment of DDH is necessary in order to reduce the recommended duration of splintage.

There were 6 cases of unstable Graf type IIc hips which were demonstrated under US after stressing the joints. They were treated by hip spica followed by Pavlik harness. Therefore, it is important to examine the stability of Graf type IIc hips under US as this will affect the treatment strategy.

The preparation stage for loosening the joint which is usually required for the older children was not needed in this study population.[2] This is because the treatment had started at early stages of life before the muscle tightness and contracture develop.[2] Patients who were diagnosed as Graf type D and Graf type III were treated by close reduction followed by retention and maturation stage. They were put in hip spica and then Pavlik harness. The

required average time for complete hip healing was 10 weeks and 16 weeks for Graf type D and Graf type III, respectively. Similarly, the required average time was found to be less for type D (8 weeks) compared to type III (16 weeks) by Marek et al.[9] Therefore the prompt use of US in young children allows us to predict the duration and type of management of DDH based on Graf classification.

Five babies were dropped out of the study because of geographical distance and logistic issues. Local skin rashes developed in 2 babies, but they were resolved after removal of the harness. At 6 months follow-up, there was no evidence of avascular necrosis and recurrence on US and X-ray in those who wore the splint. A study performed in Kyoto University/Japan, found that infants who received treatment within the first month of life did not develop avascular necrosis. However, the incidence of avascular necrosis was 16% in those subjects who were received splint after the first few months of life.[25] The primary reason for absence of avascular necrosis in those who receive treatment at an early stage may be due to the absence of soft tissue and adductors tightness which allows closed reduction without using force. Secondly, it may be due to the reason that US allows a shorter period of treatment. Therefore, it has been recommended that a period of traction is necessary in older infants with soft tissue contracture in order to avoid the risk of avascular ncrosis.[25] For this study, however, a longer period of follow-up is recommended to make sure that there is no avascular necrosis as a complication of conservative treatment.

Ultrasound is the best and most practical screening tool currently available for detection of DDH during the early months of life, because the hip joint is largely cartilaginous that cannot be seen on X-ray and US has no known side effects. Furthermore, ultrasound can detect DDH in babies with normal physical examination. Similarly, babies with normal hips may have clinical instability. In addition, ultrasound can be used successfully for follow up until the age of 6 months in order to show the response to treatment because it is more reliable than physical examination.

Ultrasound is recommended for newborn babies (particularly those with risk factors) as the initial screening and follow-up tool for DDH. However, a randomized control study is recommended to determine the role of universal US versus selective US in reducing the incidence of missed DDH cases. Subsequent evaluation of the cost effectiveness of national US screening using appropriate economic analysis is similarly recommended.

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پوختە

رۆ لی سۆنار بە بەراورد لەگەڵ پشکنینی کلینیکی لە دەستنیشان کردن و چارەسەرکردنی دەرچونی جومگە ی کڵۆتی زگما کی لە شە ش مانگی یەکە می دوای لە دایك بوون

پێشەکی و ئارمانج: جومگەی کڵۆتی مندال زیاتر پێکهاتیە لە کرکراگە لە شەش مانگی یەکەمی ژیان. بۆیە بەکارهێنانی (سۆنار) شەپۆلەکانی سەروی دەنگ بۆ دەستنیشان کردنی سەرەتایی نەخۆشی لەجێچونی جومگەی کڵۆتی زگما کی (DDH) گرنگی زیاتر دەبێت. چونکە گەشەی جومگەی کڵۆت خێرا تر لە سێ مانگی یەکەمی ژیان، بۆ یەچارەسەرکردنی لە تە مە نێکی زوو دەرئەنجامێکی باشتری دەبێت. بۆیە پێویستی بە دەستنیشان کردن و چارەسەرکردنێکی خێرا هەیەبۆ لەجێچونی جومگەی کڵۆتی زگما کی. ئامانج لەم توێژینەوەیە نرخاندنی رۆ لی سۆنار بە بەراورد لەگەڵ پشکنینی کلینیکی لە دەستنیشان کردنی نەخۆشی لەجێچونی جومگەی کڵۆتی زگما کی لە 0–6 هەفتەی یەکەمی ژیان. وەهەروەها دەستنیشان کردنی رۆ لیان لە هەلسەنگاندنی دەرئەنجامی چارەسەرکردن لە 6 مانگی یەکەمی ژیاندا.

ریکێن ئەکولینێ: 150 منداڵی ساوا پشکنینیان بە سۆنار بۆ کرا بۆ نەخۆشی لەجێچونی جومگەی کڵۆتی زگما کی، ئەو جومگانە پۆلین کران بەپێی جۆرەکانی گراف. پاشان چاودێری کرا ن بە سۆنار بۆ پیشاندانی کاریگە ری چارەسەرکردن.

ئەنجام: نا وەرا ستی تەمەنی منداڵەکان لەکاتی دەستنیشان کردنی سەرەتایی بە سۆنار 4 هەفتە بوو. لەنێوان ئەوانەی ئەم نەخۆشییەیان هە بوو بە سۆنار، تە نها 38,5٪ یان دەستنیشان کران بەپشکنینی کلینیکی. پەیوەندیەکی بەرچاو هەبوو لەنێوان لەجێچونی جومگەی کڵۆتی زگما کی و هەبونی هۆکارە ترسناکەکان بۆئەم نەخۆشییە (p کێمتر ژ0,05). لە کاتی 6 مانگی بەدواداچوندا 30 منداڵ نەخۆشی لەجێچونی جومگەی کڵۆتییان هە بوو و گشتیان چارەسەرکران بەڵام بە ماوەی جیاواز. هیچ دەرئەنجامی خراب نەبوو تا تەمەنی 6 مانگی بەدواداچون.

دەرئەنجام: بەکارهێنانی سۆنار بۆ دەستنیشان کردنی سەرەتایی نەخۆشی لەجێچونی جومگەی کڵۆتی زگما کی باشترین ئامێری بەردەستە. هەروەها دەتوانرێت بەسەر کەوتو یی بەکاربهێنرێت بۆ هەلسەنگاندنی دەرئەنجامی چارەسەرکردن.

الخلاصة

دور السونار بالمقارنة مع الفحص السريري في العلاج خلع الورك التطوري خلال الأشهر الستة الأولى من العمر

خلفية واهداف البحث: يُكوِّن الغضروف الجزء الاكبر من مفصل الورك خلال الأشهر الستة الأولى من العمر. لذلك إزداد استخدام الموجات فوق الصوتية (السونار) للتشخيص الأولي لمرضى خلع مفصل الورك التطوري (DDH). لأن نضوج مفصل الورك هو أسرع خلال الأشهر الثلاثة الأولى من العمر، التدخل المبكر يوفر تكهن أفضل للمرض. بالتالي هناك حاجة مهمة للمسح الأولي والعلاج . كان الهدف من هذه الدراسة تقيّم دور السونار بالمقارنة مع الفحص السريري في التشخيص الأولي لمرض خلع الورك التطوري خلال 0 – 6 اسابيع من العمر. وعلاوة على ذلك، لتقيّم دورهمافي متابعة الاستجابة للعلاج والمراقبة لستة الأشهر الأولى من العمر.

طرق البحث: خضع 150 رضيع (5 أيام – 6 اسابيع من العمر) للفحص السريري و الفحص بالموجات فوق الصوتية لمرض خلع مفصل الورك التطوري, صنفت الحالات على انواع وفقا لتقنية غراف. و تم متابعتها لستة الأشهر الأولى من العمر لمراقبة الاستجابة للعلاج.

النتائج: معدل عمر الأطفال خلال استخدام الموجات فوق الصوتية للتشخيص الأولي كانت 4 أسابيع. فقط 38,5% من الحالات خلع مفصل الورك التطوري بالسونار كان عندهم الفحص السريري غير طبيعي. كانت هناك علاقة ملحوظة ذات دلالة إحصائية بين مرض خلع مفصل الورك التطوري ووجود عوامل الخطورة (قيمة p أقل من 0,05). خلال 6 أشهر من المتابعة، تم تشخيص30حالة من مرضى خلع مفصل الورك التطوري. تم إعادة تشكيل المفصل لجميع الحالات لكن في فترات مختلفة. ولم يحصل مضاعفات العلاج عند بلوغهم 6 اشهر.

الاستنتاجات: من الممكن لمفصل الورك أن يكون طبيعي بالفحص السريري ولكن غير طبيعي بالسونار والعكس صحيح. فحص بالسونار هي الأداء الأفضل المتاحة للتشخيص الأولي لمرض خلع مفصل الورك التطوري. وعلاوة على ذلك، يمكن أن تستخدم بنجاح لمتابعة الاستجابة للعلاج.

ENDOBRONCHIAL TUBERCULOSIS MIMING TUMOR - CASE SERIES

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Submitted 21 Jan 2011; accepted 3 Aug 2011

SUMMARY

Endobronchial tuberculosis is a mycobacterial infection of the bronchial tree, a rare form of pulmonary tuberculosis. The bronchoscopic appearances of Endobronchial tuberculosis may mimic tumor lesions. Literature review revealed few case reports and short case series from various parts of the world. This is a report of Endobronchial tuberculosis from Duhok/Iraqi Kurdistan diagnosed by bronchoscope and managed successfully with anti-tuberculous chemotherapy.

Duhok Med J 2011;5(2): 97-102.

Key words: Endobronchial Tuberculosis, Bronchoscope, Tumor

Endobronchial tuberculosis (EBTB) is defined as tuberculous infection of the tracheobronchial tree with microbial and/or histopathological evidence.[1] Bronchoscopic examination is the key for the diagnosis, CT and bronchoscope are the methods used for diagnosis and assessment of treatment options. The lesion can easily be confused with other diseases since the clinical findings are non specific.[2] The classical systemic symptoms include fever, night sweat, anorexia, weight loss and malaise. Organ-specific symptoms include persistent cough, pleuritic pain and haemoptysis.[3] Other presenting features are lobar or lung collapse, unresolved pneumonia, dyspnoea and stridor.[4] Endobronchial tuberculosis is listed as one of the serious complications of pulmonary TB, Bronchostenosis, tracheal stenosis are possible complications.[4,5] In many cases EBTB simulate lung cancer in endoscopic findings.[4,6,7] Bronchoscope is mandatory tool not only for diagnosis but also for follow up and relieving of stridor and atelectasis.[2,4,6-8]

CASE PRESENTATION

We are presenting three patients with EBTB. The presenting symptoms to some extent were similar where all of them presented with mild fever, irretative cough and two of them have haemoptysis. Radiological findings were different prominent bronchopulmonary shadow, pleural effusion and ill defined, round, non-homogenous opacity in right Middle zone (Figure 1) while CT scan of the last patient demonstrated pulmonary enhancing opacity in the apical segment of right lower lobe with cavitation, hillar and mediastinal lymphadenopathy (Figure 2), Flexible bronchoscope findings are also different were one case showed amass totally obstructing a segment (Figure 3), the second showed red congested mucosa with ulceration (Figure 4) and pedunculated fleshy mass in the 3ed case (Figure 5). Bronchial lavage and brushing were negative for acid fast basilli and cytology revealed benign bronchial cells with chronic inflammatory cells and was rich in mature lymphocytes, bronchial biopsy revealed epithelial dysplasia and underlying granulomatous inflammation in all patients.

Rigid Bronchoscope under general anesthesia done for one patient (Figure 3) with relatively larger biopsy specimens obtained for better histopathological

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assessment and to exclude neoplastic growth and it confirmed the presence of necrotizing granuloma, favoring tuberculous dysplasia with overlying epithelial cells.

Anti TB started with 4 drugs (Rifampicin, isoniazide, pyrazenamide and ethambutol) for 2 months, then rifampicin and isoniazide for the next 4 months. After about 2 months from starting the treatment there was significant lowering in ESR, with clinical and radiological improvement (Figure 6). Re-evaluation included sputum examination for acid fast bacilli and it was negative (which was already negative). Flexible bronchoscope showed no evidence of any mass in previous site with complete obstruction of that bronchus (Figure 7). No steroid was needed during the period of therapy.

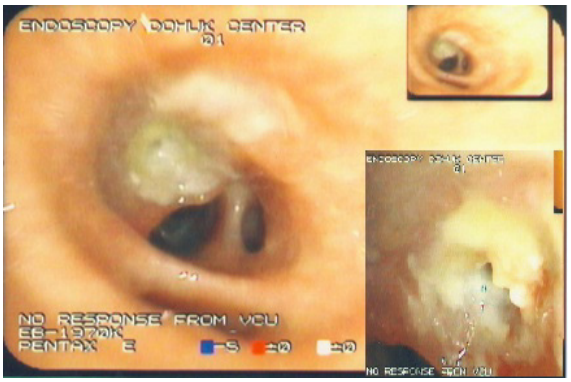

Figure 3. Mass obstructing segment

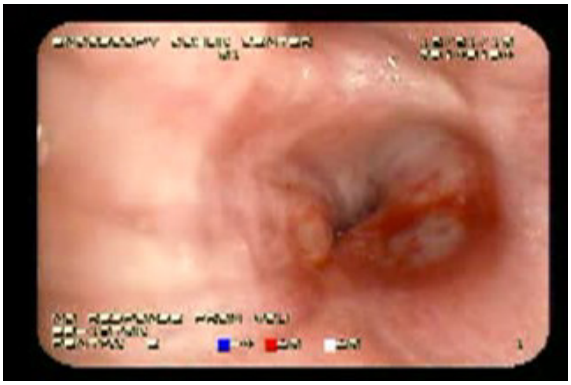

Figure 4. Ulcerating mucosa

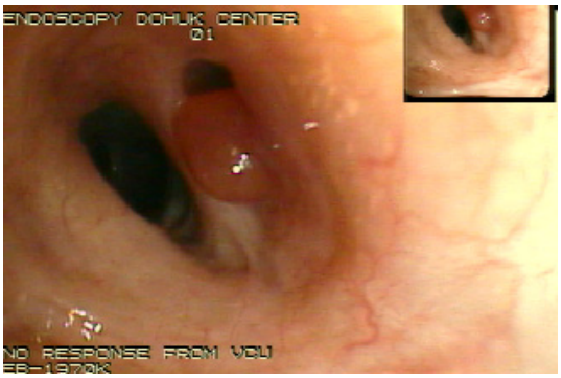

Figure 5. Pedunculated mass

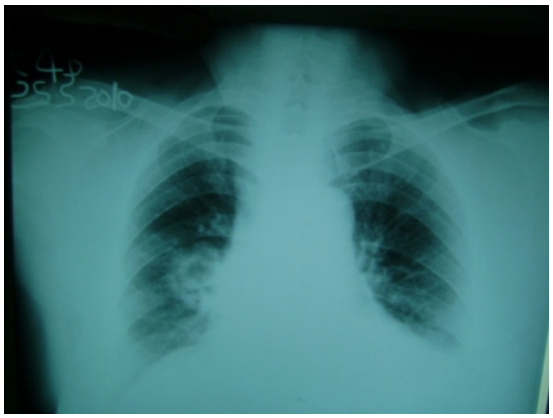

Figure 1, Chest X-Ray

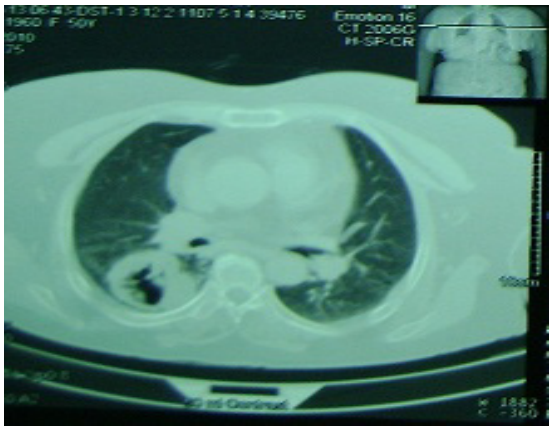

Figure 2. Chest CT scan

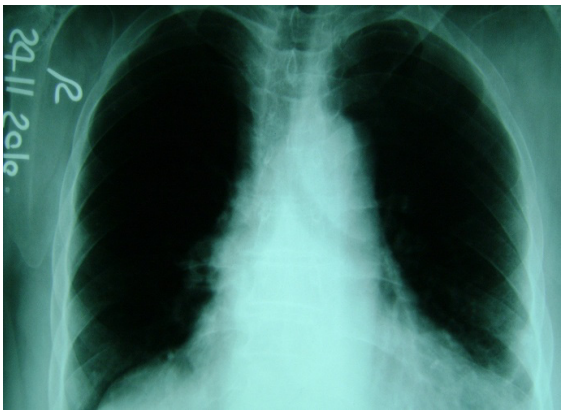

Figure 6. Chest X-ray of the same patient in figure 1 seven months later

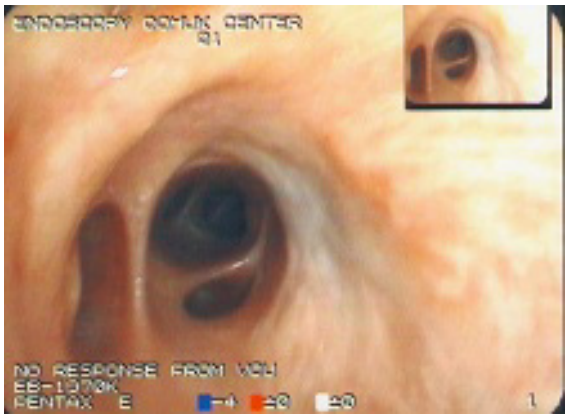

Figure 7. Bronchoscopic findings of the same patients in figure 3 seven months later

DISCUSSION

EBTB is of rare occurrence.[9] In our experience, out of 147 patients diagnosed as pulmonary tuberculosis in 2010 at the Respiratory and Thoracic Clinic in Duhok city and out of 107 patients who underwent bronchoscope in Azadi hospital bronchoscopy unit and Duhok private scope centre in the same year, only 3 patients had been diagnosed as Endobronchial tuberculosis. The presentations are somewhat similar and mostly go with non specific pulmonary infection. Our initial impression after bronchoscope examination favored a diagnosis of bronchogenic carcinoma (macroscopically appearances of the lesion by bronchoscope). Chest X-ray, CT scan and bronchoscopic findings are not specific for tuberculosis. To exclude tumors we bronchoscoped one patient using the rigid bronchoscope in whom we have a high suspicion of malignancy to obtain a larger more informative biopsy. As in the present study negative acid fast bacilli sputum and bronchial lavage does not exclude EBTB.[4,8] In our cases the diagnosis was based on histopathological findings of necrotizing granuloma as no AFB isolated from sputum or bronchial lavage. Treatment by anti TB therapy for a 6 month course revealed good response, corticosteroid were not used as their role is controversial.[1-3,6,7] The main issues are curing the patient from TB and prevent complications mainly the bronchial stenosis.[1,2,4-7] As in our cases complete healing and fibrosis of apical segment of right lower lobe in one patient and totally obstruction of its bronchus and no defect in lower lobe bronchus. No surgery had been required for any these patients. Surgery may be offered to patients with stenosis of large airway.[4] In addition to clinical, radiological and laboratory investigations, we strongly recommend using the flexible bronchoscope as part of fallow up in such patients.

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پوختە

سللا ناف بوریێن هەوای وەك پەنجەشێرا سیهێ _ زنجیرەكا حالەتا

سللا ناف بوریێن هەوای هەوەدانەكا میكروبیە بوریێن هەوای توش دبن، و ئەڤە جورەكێ هەرە كێمە ژ جورێن سللا سیها. شێوەیێ دویربینی یێ ئەڤێ سللێ دبت خوایابكەت وەك پەنجەشێرا سیهێ. رابورتێن بەلاڤكری ژمارەكا كێم ژ ڤێ نەخوشیێ توماردكەن ل سەرانسەرێ جیهانێ. ئەڤە راپورتەكە ب سللا ناف بورێن هەوای ژ پارێزگەها دهوك هەرێما كوردستانێ عیراق، هاتینە دەستنیشانكرن برێكا دویربینێ وهاتینە جارەسەركرن ب شێوەیەكێ سەركەفتی برێكا دەرمانێت سللێ.

الخلاصة

التدرن داخل القصبات المشابه للورم – سلسة حالات

التدرن داخل القصبات المشابه للورم هو عدوى جرثومية تصيب القصبات الهوائية وهو شكل نادر من التدرن الرئوي. ظهور هذا الشكل من التدرن الرئوي عن طريق الناظور يمكن ان يشابه الاورام السرطانية. المقالات المنشورة اظهرت وجود عدد قليل من الحالات في انحاء العالم. هذا المقال عن التدرن داخل القصبات في محافظة دهوك في اقليم كوردستان العراق عن الحالات المشخصة عن طريق الناظور والتي عولجت بنجاح بواسطة الادوية المضادة للتدرن.