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An echocardiographic study in patients with palpitations

Arwa M. Fuzi Alsaraf
Department of Medicine, College of Medicine, University of Mosul.

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ABSTRACT

Objectives: Palpitations (increased or abnormal awareness of the heart beats), often caused by cardiac arrhythmia, anxiety, and non cardiac causes; also caused by non arrhythmic cardiac problems such as mitral valve prolapse (MVP), other valvular disease, heart failure, cardiomyopathy, and congenital heart diseases (CHD). Some patients had no cause for palpitations.

We aim to study the cardiac problems revealed by echocardiography in patients with palpitations, and the differences between males and females.

Patients and methods: A total of 267 patients who sought medical advice specifically for palpitations, and another 173 controls, had echocardiography evaluation, results were classified into three groups, MVP, myocardial disease, and valvular and CHD. Statistical analysis using chi-square test was applied.

Results: The patients consisted of 221 (83%) females, and 46 (36%) males, aged between 14-77 years, mean age 38 years. MVP was diagnosed in 76 (28%) patients (P value 0.019) and it was more significant in females (P value 0.046). Other valvular diseases and CHD were also considerable causes of palpitations in females (P value 0.043). Myocardial diseases were diagnosed in 62 (23%) patients, including 15 (33%) males.

Conclusion: Echocardiography was normal, or minimally abnormal as in MVP in most of patients (71%). MVP and other valvular diseases and CHD were significant causes of palpitation in females, while myocardial diseases were more frequent in males. These results are consistent with previous studies.

Keywords: Palpitation, echocardiography, mitral valve prolapse, myocardial, valvular and congenital heart diseases.
By definition palpitation is abnormal, unpleasant awareness of one’s own heart beat. This symptom may be brought on by a variety of cardiac disorders, such as cardiomyopathy, heart failure, valvular heart diseases, coronary heart diseases and pericarditis, but the most common cause is primary cardiac arrhythmias (1-3). Several non cardiac disorders such as hyperthyroidism, vasovagal syncope and hypoglycemia may also cause palpitation (1, 2). No cause for palpitation can be found in up to 16% of patients (1, 4).

Palpitation is one of the common symptoms for which cardiac patients are referred. It may be the reason for 30 to 40% of referral to cardiology clinics like dyspnea (3,5,6). Palpitation can either be a physiological expression of normally beating heart or dangerous pathological state of the heart. This makes this symptom unique and warrants careful evaluation.

The heart is a mechanical organ with multiple mobile anatomical structures. There is constant blood flow in multiple directions. Apart from this, the heart has its unique translational, rotational movement. These intrinsic movements combined with proximity to chest wall generate vibratory motion signals. These signals are generally dampened by the encircling pericardial space. The neural signals responsible for perception of palpitation are not clear. If the heart hits against the chest wall it is the somatic nerve from the chest wall that carries the signal. Vibrations generated within the heart chambers and the valves are carried by the myocardial and intravascular autonomic nerves (7).

Historically “Harvey” used the word palpitation in De Motu in reference to a motion of the heart observed in his vivisection studies. Moving beyond his physiological observation, he expressed awareness that strong emotions have a physical effect on the body manifested in the behavior of the heart: “for every passion of the mind which troubles men’s spirits, either with grief, joy hope or anxiety, and gets access to the heart, there makes it to change from its natural constitution, by distemperature, pulsation, and the rest (8, 9).” Lower used the term to describe a symptom complex in a physiological setting, an important distinction. The interdependence of brain and heart is a recurrent theme in Lower’s work (9, 10).

Approximately 15% of the general population experience palpitations in a given year (11, 12). Palpitations are typically encountered in outpatient settings, reportedly ranking among the top 10 symptom complain of patients attending a general internal medicine clinic (12). Palpitation may be brought on by a variety of cardiac disorders, such as cardiomyopathy, valvular heart disease, and coronary artery disease, but the most common cause is primary cardiac arrhythmias, several non cardiac disorders may also cause palpitations.

For several decades a widely held belief has existed in some association between MVP and various cardiac symptoms, including palpitations (12). In MVP (billowing of mitral valve leaflet into the left atrium during systole), although most patients are asymptomatic, some experience nonspecific symptoms (e.g. chest pain, dyspnea, palpitations, dizziness, near syncope, migraine and anxiety), thought to be due to poorly defined associated abnormalities in adrenergic signaling and sensitivity rather than to MVP alone. In about one third of patients, emotional stress precipitates palpitations which may be a symptom of benign arrhythmias (13). Transient MVP may occur when intravascular volume
decreases significantly as in severe dehydration or during pregnancy when the woman is recumbent and the gravid uterus compresses the inferior vena cava reducing venous return (13).

The resting electrocardiogram should be performed in all patients with palpitation. Obviously, a palpitation is not likely to be "caught" during the brief recording period of an ECG. However the resting ECG provides important clues as to the presence or absence of underlying structural heart disease which can provide a substrate for arrhythmias (12). Exercise testing in patients with palpitations who also have chest pain may help in uncovering evidence of ischemic heart disease, which in turn, might be contributing to the patients' symptoms; also it may induce suspected arrhythmias in patients with palpitations. Holter recording can be helpful in patients who experience their palpitations at least once per day.

Echocardiogram can be very useful in ruling in or ruling out overt structural heart disease.

In our study we aim to verify the echocardiography findings in different patients with palpitations, and to clarify the role of structural heart disease in causing palpitation. The difference between male and female with palpation in regard to the presence of underlying structural heart disease is also studied.

Patients and methods

This observational, hospital based, retrospective, case control study began in January 2010 and ended in March 2011. Four hundreds and forty cases and controls aged between 13 and 77 years were involved.

Study sample and data collection

Two hundreds and sixty seven (267) male and female patients presented with palpitations aged between 14 and 77 years were recruited from outpatient's clinic in Ibn Sina Teaching Hospital in Mosul. Another group of 173 male and female controls, aged between 13 and 70 years, who had echocardiography study for routine checking, preoperative preparation or other non specific symptoms (like chest discomfort, mild dyspnia, atypical chest pain, cardiac neurosis) but without palpitation were collected from echocardiography unit in the same hospital.

Consents of patients were insured, then thorough history was taken including: history of the palpitation described as (heart flips, skipped beats, strong beats, irregular beats, heart thumping, bubble sensation in heart or chest, heart fluttering, racing or rapid heart beats, pounding in chest or neck, heart jumping out of chest and chest shaking) (12); physical examination, electrocardiography study and chest X-ray were performed. Detailed 2- dimensional, M-mode and Doppler echocardiography study was carried on for all patients and controls. Accordingly, the candidates were classified into 4 groups: those with normal echocardiograph considered as normal, those with MVP (defined as movement of part of either leaflet behind the plane of the annulus in any view other than the 4- chamber view, or the displacement of the point of coaption behind the plane of annulus in the 4- chamber view) (14), considered as MVP group, those with left ventricular (LV) systolic dysfunctions (ejection fraction < 50%), diastolic dysfunctions, left or right ventricular hypertrophy, cardiomyopathies and LV segmental wall motion abnormalities were considered as ischemic and non ischemic myocardial diseases MCD group, and valvular heart diseases (excluding MVP) and congenital heart disease considered as V/CHD group.

Statistical analysis

Chi – square test was performed to determine the (P-value), p- value < 0.05 was considered significant. Odd ratio (OR) that is (odds of factor among cases divided by odds of factor among control) was calculated, 1 means no risk, >1 means risk, <1 indicates protection. Confidence interval (CI) was considered for all values.

Results

A total of 267 patients presented with palpitations were included in the study, age was between 14 and 77 years, with a mean age 38 years (14 SD). There were 221 female
patients (83%) and 46 male patients (17%), female: male ratio 4.8: 1. (Table 1)

One hundred seventy three controls without palpitation were collected aged between 13 and 70 year old; mean age 39 year (12 SD), 111 females (64%) and 62 males (36%), female: male ratio 1.8: 1. (Table 2)

Abnormal echocardiography including MVP was found in 154 patients presented with palpitation (58%), and in 89 (51%) controls, P value (0.199), including126 female (57%), and 28 (60%) males. (Table 2)

MVP was diagnosed in 76 (28%) patients with palpitation, and in 31 (17%) controls, (P value 0.019). Sixty two patients (23%) with palpitation found to have cardiac muscle disease (including ischemic cardiac muscle diseases), compared to 53 (30%) controls, (P value 0.554). Valvular or congenital heart disease was detected in 16 patients with palpitation (6%), and in 5 (3%) controls, (P value 0.095). (Table 4)

In other point of view structural heart diseases other than MVP were counted in 78 (29%) patients with palpitations, 61 (28%) females and 17 (37%) males. and in 58 (34%) of controls. (Table 3).

The difference in types of underlying structural heart diseases between males and females was shown in (table 4). MVP and other valvular or congenital heart diseases were the cause of palpitation in 65 (29%) and in 14 (6%) females respectively with a P value (0.046) and (0.043). Myocardial diseases found in 47 (21%) females with palpitation. Ninety five (43%) females with palpitation had normal echocardiography study.

In males, MVP cause palpitation in 11 (24%) patients, myocardial diseases in 15 (33%) patients, and other valvular or congenital heart diseases in 2 (4%) patients. Normal echocardiography was found in 26 (57%) male patients.

Table (1): Percentage of male and female in patients and controls.

<table>
<thead>
<tr>
<th>Gender</th>
<th>Palpitation</th>
<th>Control</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>221</td>
<td>111</td>
<td>332</td>
</tr>
<tr>
<td>Male</td>
<td>46</td>
<td>62</td>
<td>108</td>
</tr>
</tbody>
</table>

Table (2): Total patients with structural cardiac abnormalities including MVP compared to normal echo study.

<table>
<thead>
<tr>
<th>Echo study</th>
<th>Palpitation 267</th>
<th>Control 173</th>
<th>OR</th>
<th>CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>F 221</td>
<td>M 46</td>
<td>F 111</td>
<td>M 62</td>
<td>1.29</td>
</tr>
<tr>
<td>Cardiac abnormality and MVP</td>
<td>154 58%</td>
<td>89 51%</td>
<td>1.45</td>
<td>1.12</td>
<td>0.9-2.3</td>
</tr>
<tr>
<td>Normal</td>
<td>113 42%</td>
<td>84 49%</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>95 43%</td>
<td>84 49%</td>
<td>1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

P value 0.00.
Table (3): Patients with significant structural heart diseases, compared to normal and MVP.

<table>
<thead>
<tr>
<th>Echo study</th>
<th>Palpitation 267</th>
<th>Control 173</th>
<th>OR</th>
<th>CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>F</td>
<td>221</td>
<td>111</td>
<td>F</td>
<td>M</td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>46</td>
<td>62</td>
<td>M</td>
<td>F</td>
<td></td>
</tr>
<tr>
<td>Cardiac abnormality</td>
<td>78 29%</td>
<td>58 34%</td>
<td>0.82</td>
<td>0.54-1.24</td>
<td>0.339</td>
</tr>
<tr>
<td></td>
<td>61 28%</td>
<td>17 37%</td>
<td>0.98</td>
<td>0.76</td>
<td>0.95-1.63</td>
</tr>
</tbody>
</table>

Table (4): Percentage of types of echocardiography abnormalities in patients and controls compared to normal echo study.

<table>
<thead>
<tr>
<th>Risk factors (Echo study)</th>
<th>Palpitation</th>
<th>Control</th>
<th>OR</th>
<th>CI</th>
<th>P -value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MVP</td>
<td>fem</td>
<td>65</td>
<td>22</td>
<td>19.8%</td>
<td>1.55</td>
</tr>
<tr>
<td></td>
<td>male</td>
<td>11</td>
<td>9</td>
<td>14.5%</td>
<td>1.77</td>
</tr>
<tr>
<td>MCD</td>
<td>fem</td>
<td>47</td>
<td>29</td>
<td>26.2%</td>
<td>0.99</td>
</tr>
<tr>
<td></td>
<td>male</td>
<td>15</td>
<td>24</td>
<td>38.5%</td>
<td>0.90</td>
</tr>
<tr>
<td>V/CHD</td>
<td>fem</td>
<td>14</td>
<td>2</td>
<td>1.8%</td>
<td>4.27</td>
</tr>
<tr>
<td></td>
<td>male</td>
<td>2</td>
<td>3</td>
<td>4.8%</td>
<td>0.96</td>
</tr>
<tr>
<td>Normal</td>
<td>fem</td>
<td>95</td>
<td>58</td>
<td>52.2%</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>male</td>
<td>18</td>
<td>26</td>
<td>42%</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>267</td>
<td>173</td>
<td></td>
<td></td>
<td>267 173</td>
</tr>
</tbody>
</table>

MVP = mitral valve prolapse, MCD = myocardial disease, V/CHD= valvular or congenital heart diseases, total P= total patients with palpitations, total C= total controls, OR: odd ratio, CI: confidence interval.

Discussion

In our study the palpitation was 4 times more common in females (83%); this result is slightly more than the ratio described by Summerton et al study (67%) (15). Palpitations occur frequently in women at all ages, especially during the luteal phase of the menstrual cycle, during pregnancy, and during the perimenopausal period. A correlation between ovarian hormones and occurrence of paroxysmal supraventricular tachycardia has been reported in female patients with normal menstrual cycle (2). Palpitation is frequently reported in cases of mitral valve prolapse, whereas episodes of supraventricular tachycardia reported during pregnancy may be due to mechanical stimuli or to a suggested arrhythmogenic effect of pregnancy. Palpitations during perimenopausal period are usually benign and seem to be related to the increased sympathetic activity (2).

Significant structural cardiac diseases were discovered in 61 (28%) females compared to 17 (37%) male patients, apparently males with palpitation are more likely to have serious cardiac disorders than females; this is consistent with Weber and Kapoor study which showed that male sex is an independent predictor of a cardiac etiology for palpitation (3).
4, 16). Overall serious structural heart disease found in 78 (29%) patients with palpitation has no statistical significance compared to 58 (34%) in the control group, which is relatively a high percent, this is because patients with other presentations like dyspnea and chest pain but without palpitation were included in the control group.

The result of one study (17) of 24-hour ECG monitoring showed that ventricular tachycardia was associated with previous myocardial infarction, idiopathic dilated cardiomyopathy, significant valvular lesions, and hypertrophic cardiomyopathies (18). So diagnosing these disorders in patients with palpitation by conducting echocardiography is important because it may notify serious arrhythmias. MVP has been found to be the most common valvular cardiac anomaly in developed countries. Hospital based studies, some with flexible criteria for diagnosis put the prevalence of MVP between 5 to 35%, another study shows the incidence of clinically significant MVP is between 3 to 8%; females affected more than males with 2:1 ratio (19).

In our study MVP was diagnosed in 76 (28%) patients with palpitation compared to 31 (17%) controls (P value 0.019). It was a significant cause of palpitation in females (P value 0.046), but not in males, (P value 0.29). This is consistent with findings of some other studies. In the (study of Framingham offspring), more distinct criteria for diagnosis of MVP were used and showed the incidence of MVP in the general population is about 3%, with no significant difference in men versus women (20). The relatively high percentage of MVP in controls in our study (17%) was probably due to inclusion of patients with other symptoms like dyspnea and non specific chest pain in control group. Virtually every type of supraventricular arrhythmias, as well as ventricular premature depolarizations and nonsustained ventricular tachycardia, has been described with MVP and palpitations are nearly ubiquitous in this disorder (21).

Myocardial disorders (including left and right ventricular dilatation, hypertrophy, systolic and diastolic dysfunctions, segmental wall motion abnormalities and ischemic cardiac muscle diseases), were found in 62 (23%) patients with palpitation, compared to 62 (36%) controls, (P value 0.55). Palpitation was a less frequent presentation of myocardial disorders and the control group who had complained of dyspnea had more evidence of these disorders. Patients with dilated cardiomyopathy or congestive heart failure rarely feel their heart beat during exertion; instead they have dyspnea as the LV force of contraction is less (7). Palpation may indicate a hyperkinetic state of the heart (anxiety, anemia, fever, thyrotoxicosis, pregnancy etc). So LV EF is normal or above normal. So presence of palpitation could be an indirect evidence of reasonably good LV function (7). Although palpitations are uncommon in patients with LV dysfunction, they indicate more serious arrhythmia (17).

Significant valvular and congenital heart diseases was found in a small percentage 16 (6%) patients with palpitation (P value 0.095), which was significant in females (P value 0.043) but not in males (P value 0.97).

Overall, patients with palpitation were not more likely to have serious abnormal echocardiography than control patients.

**Conclusion**

The echocardiography study is not indicated in most patients with palpitation, unless associated with other cardiac symptoms or serious arrhythmias.

Further clinical studies are recommended to correlate the types of palpitations, categories of patients and presence of other diseases with the ECG findings and the echocardiography study in patients with palpitations.

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7. Venkatesan S MD. Palpitation, some observations: expressions in cardiology 2008; 2: 22
Polycythaemia: a clinico-haematological study

Faris Y. Bashir*, Abdul-Kadder S. Ahmed**
* Department of Pathology, College of Medicine, University of Mosul;
** Department of Oncology, Oncology and Nuclear Medicine Hospital, Mosul.

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ABSTRACT

Objectives: (1) To assess the prevalence of primary and secondary polycythaemia in our locality and their detailed clinical and haematological parameters. (2) To determine causes of secondary polycythaemia. (3) To establish a working formula for determining packed cell volume reduction after a given number of blood units donated.

Methods: A prospective clinico-haematological case series study, done in Mosul teaching hospitals and central blood bank, including seventy two patients with raised packed cell volume. The patients were assessed by clinical evaluation, complete blood picture, coagulation tests, chemical tests, chest x-ray, echocardiography, ultrasound, in addition to arterial O2 saturation and pulmonary function tests.

Results: The most common clinical features were headache, dizziness and plethora. The pruritus was present only in polycythaemia vera. Thrombotic complications present more in secondary polycythaemia. Raised packed cell volume and haemoglobin above normal value has been found in all patients. Leucocytosis and thrombocytosis was present in 12/42 patients with polycythaemia vera. Majority of patients with secondary polycythaemia (86.7%) have ventilatory defects. The effect of number of blood units donated and it’s frequency (in weeks) on the degree of packed cell volume reduction in patients treated with venesection was expressed by equations.

Conclusions: Polycythaemia vera patients were younger than those with secondary polycythaemia and found mainly to affect males. All cases of secondary polycythaemia were due either to chronic lung disease or congenital heart disease. We have established an equation when applied to patients with polycythaemia can predict value of packed cell volume reduction after donating a given number of blood units.

Keyword: Polycythaemia.
Polycythemia is defined as a number of conditions characterized by raised packed cell volume; (PCV > 0.51 L/L in males and > 0.48L/L in females). These conditions may be divided into two groups on the basis of the red cell mass (RCM) findings:(1)

I. Absolute polycythemia. (RCM raised):
   A. Polycythemia vera.
   B. Secondary polycythemia.
   C. Idiopathic erythrocytosis.

II. Apparent polycythemia. (RCM within normal range).

Polycythemia vera (PV) is a chronic, progressive and ultimately fatal disease, in which the fundamental abnormality is an excessive production of the formed elements of the blood by a hyperplastic bone marrow. The marrow hyperplasia is not secondary to any recognized bone marrow stimulus, and at present the cause is unknown. No increase of plasma erythropoietin has been demonstrated (2). Plasma level of this hormone are reduced in PV patients, and PV progenitor cells, unlike normal ones, can survive in vetro and give rise to erythroid colonies (BFU-E) in the absence of added erythropoietin (endogenous erythroid colonies).(3)

In 2005, several groups identified a unique acquired mutation in cytoplasmic tyrosine kinase JAK2 in myeloid cells from the great majority of patients with PV.(3)

Secondary Polycythemia is defined as an absolute increase in the red cell mass may arise from a wide variety of causes:(1)

1. Polycythemia secondary to hypoxia:  
   a) High altitude polycythemia(9).  
   b) Hypoxaemic lung disease(1,5).  
   c) Cyanotic congenital heart disease(6).  
   d) Smoker's polycythemia(7).  
   e) Methaemoglobinaemia (1).  
   f) Chemically induced tissue hypoxia(8).

2. Secondary polycythemia with inappropriate erythropoietin secretion:  
   a) Renal polycythemia.(9-12)  
   b) Polycythemia with connective tissue tumours(13).  
   c) Brain tumours(14).  
   d) Hepatoma.  
   e) Endocrine disorder(15).  
   f) Neonatal polycythemia(16).  
   g) Familial and congenital polycythemia (17,18).

Patients and methods

During the period between December 2003 and July 2004, seventy two patients with raised packed cell volume (PCV>0.51 L/L in males and >0.48L/L in females), were studied from Mosul teaching hospitals and central blood bank, (61) males and (11) females. Their age ranged between (24-77) years, with a mean age of (50.4) years. After taking history, the patients were examined clinically and haematologically.

Ten ml of venous blood sample were obtained to perform complete blood picture, coagulation tests (prothrombin time, activated partial thromboplastin time) and chemical
tests. Arterial Oxygen Saturation (SaO₂) was
done using pulse oximeter (Kontron- 7840),
Pulmonary function tests using (Discom-14),
chest x ray, abdominal ultrasound were also
done. The main diagnostic criteria used in this
study were:
A. Raised PCV above 0.51 L/L in males and
above 0.48 L/L in females for diagnosing
polycythaemia.
B. Arterial O₂ saturation (Sa O₂) > 92% was
used to diagnose primary polycythaemia
and Sa O₂ < 92% was used to diagnose
secondary hypoxic polycythaemia(1).

Results
The study included 42 patients diagnosed as
PV, the age ranged between (24-77) years,
with M:F ratio of 13:1. Thirty cases were
diagnosed as secondary polycythaemia, the
age ranged between (24-75) years, with M: F
ratio of 2.8:1.
In PV 81% were below 55 years, and only
19% were equal or above 55 years. In
secondary polycythaemia 46.6% were below
55 years, and 53.4% were equal or above 55
years.
Clinical features showed headache,
dizziness, visual disturbance, plethora and red
conjunctiva as the commonest features in
most patients. There was statistically
significant difference between PV and
secondary polycythaemia regarding the
following features:
Pruritus was present in 19% patients with PV
while this feature was not present in any
patient with secondary polycythaemia
(P<0.05).
Splenomegaly was present in 35.7% patients
with PV and only in one patient with secondary
polycythaemia (P<0.01). There was no
significant correlation between Splenomegaly
and PCV levels.
Thrombotic complications (Table 1) were
present in 11.9% patients with PV and in
36.7% patients with secondary polycythaemia
(P<0.05). The risk for thrombosis increase
with age from 25% in patients younger than 55
years to 75% in those equal or above 55 years
(Fig.1), and with increased PCV levels (Fig. 2).
Pulmonary function tests showed that the
majority of patients with secondary
polycythaemia 86.7% had ventilatory defects
compared to 14.3% in PV (P<0.001). Table 2
shows the main causes of secondary
polycythaemia.
Haematological findings showed raised PCV
above 0.51L/L in males and above 0.48L/L in
females were used as main criteria for
diagnosing polycythaemia in this study. High
Hb level above normal values has been found
in all patients. Leucocytosis and
thrombocytosis was present in 12/42 patients
with PV. The red cell morphology was
normochromic normocytic, few cases were
normochromic normocytic/macrocytic. Basophil-
ilia was not found in any patients. 80% of
patients presented with ESR levels between
(0-2) mm/hr. PT and APTT were normal in all
patients.
Hyperuricaemia was present in 21% of patients with PV and in 37% of those with secondary polycythaemia, the risk of hyperuricaemia in these patients increased with increasing PCV levels. The effect of number of blood units donated and its frequency (in weeks) on the degree of PCV reduction in patients treated with venesection was expressed by the following equations (Table 3,4):

A: In patients with primary polycythaemia:
PCV reduction L/L = 0.0496-0.00214 (weeks) + 0.0248 (No. of blood units donated).

B: In patients with secondary polycythaemia:
PCV reduction L/L= 0.0034-0.00721 (weeks) + 0.0538 (No. of blood units donated).

Table (1): Clinical features of the patients.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Primary polycythaemia</th>
<th>Secondary polycythaemia</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total No.=(42)</td>
<td>Total No.=(30)</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>41(97.6)</td>
<td>30(100.0)</td>
<td>NS</td>
</tr>
<tr>
<td>Dizziness</td>
<td>32(76.2)</td>
<td>24(80.0)</td>
<td>NS</td>
</tr>
<tr>
<td>Visual disturbance</td>
<td>19(45.2)</td>
<td>14(46.7)</td>
<td>NS</td>
</tr>
<tr>
<td>Pruritus</td>
<td>8(19.0)</td>
<td>0(0.0)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Smoking</td>
<td>21(50.0)</td>
<td>17(56.7)</td>
<td>NS</td>
</tr>
<tr>
<td>Plethora</td>
<td>37(88.1)</td>
<td>24(80.0)</td>
<td>NS</td>
</tr>
<tr>
<td>Red conjunctiva</td>
<td>42(100.0)</td>
<td>30(100.0)</td>
<td>-</td>
</tr>
<tr>
<td>Hypertension</td>
<td>22(52.4)</td>
<td>12(40.0)</td>
<td>NS</td>
</tr>
<tr>
<td>Hepatomegaly</td>
<td>0(0.0)</td>
<td>4(13.3)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>15(35.7)</td>
<td>1(3.3)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td></td>
<td>12/15 palpable</td>
<td>by U/S only</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3/15 by U/S only</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombotic</td>
<td>5(11.9)</td>
<td>11(36.7)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>complications</td>
<td>4/5 CVA</td>
<td>3/11 CVA</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1/5 coronary</td>
<td>8/11 coronary</td>
<td></td>
</tr>
<tr>
<td>Bleeding tendency</td>
<td>4(9.5)</td>
<td>2(6.7)</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>3/4 Epistaxis</td>
<td>1/2 Bruises.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1/4 Bruises</td>
<td>1/2 Haematemesis.</td>
<td></td>
</tr>
</tbody>
</table>

Table (2): Causes of secondary polycythaemia.

<table>
<thead>
<tr>
<th>Secondary polycythaemia No.=30</th>
<th>Congenital heart disease No. = 4 (13.3%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung disease No. = 26 (86.7%)</td>
<td>1. Tetralogy of Fallot: No. = 2 (50.0%)</td>
</tr>
<tr>
<td>1. Chronic obstructive airways</td>
<td>2. Atrial septal defect: No. = 1 (25%)</td>
</tr>
<tr>
<td>disease (COAD) No. = 19 (73.1%)</td>
<td></td>
</tr>
<tr>
<td>a: Chronic bronchitis. (14)</td>
<td>3. Patent ductus arteriosus: No. = 1 (25%)</td>
</tr>
<tr>
<td>b: Bronchial asthma. (4)</td>
<td></td>
</tr>
<tr>
<td>c: Bronchiectasis. (1)</td>
<td></td>
</tr>
<tr>
<td>2. Obesity hypoventilation</td>
<td></td>
</tr>
<tr>
<td>syndrome No. = 4 (15.4%)</td>
<td></td>
</tr>
<tr>
<td>3. Fibrosing alveolitis No. = 2</td>
<td></td>
</tr>
<tr>
<td>(7.7%)</td>
<td></td>
</tr>
<tr>
<td>4. Mixed fibrosing alveolitis</td>
<td></td>
</tr>
<tr>
<td>and obesity hypoventilation</td>
<td></td>
</tr>
<tr>
<td>syndrome No. = 1 (3.8%)</td>
<td></td>
</tr>
</tbody>
</table>

* Obesity hypoventilation syndrome:
- (Morbidly obese BMI>40.0 with hypoxaemia)\(^{[6]}\).
- BMI (Body mass index)= weight /height\(^2\) (in Kg/m\(^2\))\(^{[7]}\).
Table (3): Effects of No. of blood units donated and the time on PCV reduction in primary polycythaemia.

<table>
<thead>
<tr>
<th>No. of blood units donated</th>
<th>PCV reduction L/L</th>
<th>1 week</th>
<th>2 weeks</th>
<th>3 weeks</th>
<th>4 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0.072</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>0.097</td>
<td>0.095</td>
<td>0.093</td>
<td>0.091</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>0.121</td>
<td>0.119</td>
<td>0.117</td>
<td>0.115</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>0.146</td>
<td>0.144</td>
<td>0.142</td>
<td>0.140</td>
<td></td>
</tr>
</tbody>
</table>

The above data was obtained from the equation:

\[
\text{PCV reduction L/L} = 0.0496 - 0.00214 \times \text{weeks} + 0.0248 \times \text{No. of blood units donated}.
\]

Table (4): Effects of No. of blood units donated and the time on PCV reduction in secondary polycythaemia.

<table>
<thead>
<tr>
<th>No. of blood units donated</th>
<th>PCV reduction L/L</th>
<th>1 week</th>
<th>2 weeks</th>
<th>3 weeks</th>
<th>4 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0.05</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>0.103</td>
<td>0.096</td>
<td>0.089</td>
<td>0.082</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>0.157</td>
<td>0.150</td>
<td>0.143</td>
<td>0.135</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>0.211</td>
<td>0.204</td>
<td>0.197</td>
<td>0.189</td>
<td></td>
</tr>
</tbody>
</table>

The above data was obtained from the equation:

\[
\text{PCV reduction L/L} = 0.0034 - 0.00721 \times \text{weeks} + 0.0538 \times \text{No. of blood units donated}.
\]

Discussion

In PV the age ranged between (24-77) years with a mean of 48 years. This is quite expected as PV is a disease of the middle and later years of life, with a wide range of distribution from adolescence to old age\(^{(19)}\). Sex distribution showed male to female ratio of 13:1, this result shows very high male predominance which does not agree with that reported in other studies which reported that males are affected slightly more frequently than females\(^{(1,19,20)}\). The increased prevalence of PV among males in the present study may be attributed to small sample size, short period of study and more frequent PCV checking among males than females particularly before blood donation in central blood bank which may reveal subclinical form of the disease in males.

In secondary polycythaemia the age ranged between (24-75) years with a mean of 54 years. This was expected as the main cause of secondary polycythaemia in this study was chronic obstructive airway disease (COAD) which manifests itself in late adult life\(^{(21)}\). Sex distribution showed male predominance with M:F ratio of 2.8:1, and this is also expected as the majority of COAD patients are smokers\(^{(21)}\), and cigarette smokers in the present study were only seen in males.

The main clinical features in PV patients in the present study were: headache, dizziness, plethoric facies, red conjunctiva, visual disturbance, hypertension, splenomegaly and pruritus. Some cases present with thrombotic complications and bleeding tendency. These features are in conformity with that of well-known reports\(^{(1,19)}\).

Pruritus was only found in PV and absent in secondary polycythaemia. This may support the fact that pruritus is attributed to increased histamine release by granulocytes\(^{(1,8)}\).

Splenomegaly was not related to increased PCV levels. This may indicate that splenic enlargement in PV was not due to expanded blood volume, this result agrees with that of other studies\(^{(19)}\).

A statistically significant higher percentage of thrombosis 36.7% has been found in our secondary polycythaemic patients. This may be attributed to the age of the studied patients as the risk for thrombosis increases with age\(^{(20)}\). Figure 4 may indicate that aggressive treatment of polycythaemia in high risk patients would be associated with a reduced risk for thrombosis.

Hepatomegaly has been reported in PV\(^{(22)}\). In the present study it was not reported and this may be attributed to small sample size included in this study. Four cases with secondary polycythaemia presented with hepatomegaly and this may be attributed to COAD associated with cor pulmonale (congestive Hepatomegaly)\(^{(23)}\).
Bleeding and bruises are reported in 9.5% of PV patients, higher percentage 25% was reported in other studies\(^{(24)}\).

The present study demonstrates that chronic lung disease and congenital heart disease are the only causes for secondary polycythaemia. This finding agrees with the result of most works in this field of study which reported that the great majority of cases of secondary polycythaemia are due to a disorder which causes a lowering of the arterial oxygen saturation of the blood (Hypoxic secondary polycythaemia).

The majority of our secondary polycythaemic cases showed ventilatory defect, this was expected as the main cause of secondary polycythaemia in the present study was found to be lung disease (Table 2). These results agree with other studies which reported that hypoxia caused by COAD is one of the most common causes of secondary polycythaemia\(^{(25)}\).

High Hb level above normal values has been found in all patients, this is quite expected as all patients included in this study were polycythaemic. Thrombocytosis and leucocytosis were the main findings in PV patients included in this study\(^{(12/42)}\), higher percentage has been reported in most of other studies\(^{(1,8,25)}\). A statistically significant difference has been found between PV and secondary polycythaemia regarding these two parameters and this is expected as PV is a panmyelosis and there is over production of granulocytes and platelets\(^{(25)}\).

The red cell morphology in the present study was normal with occasional macrocytosis. Similar observation was noticed by other studies\(^{(1,2)}\). Basophilia was not reported in any of the studied patients, and this does not agree with the result of most other studies which showed that peripheral blood basophile numbers may be modestly increased in PV\(^{(1,25)}\). This may be attributed to small sample size, or unique feature of our studied patients. ESR levels in the majority of the studied patients was low ranging from 0-2 mm/hr. PT and APTT are normal in all studied patients. These result are in accordance with most other studies\(^{(1,2,8)}\).

In PV 21% patients present with hyperuricaemia. This was expected as there was excessive cellular proliferation in this disease result in increased synthesis and degeneration of nucleoprotein and production of increased amount of uric acid\(^{(19)}\).

In secondary polycythaemia 37% patients present with hyperuricaemia and this may suggest a causative role of medication used especially diuretics and low dose aspirin\(^{(26,27)}\). These two drugs are used by large proportion of our patients in combination with other antihypertensive drugs as 40% of our secondary polycythaemic patients are hypertension.

**Conclusions**

1. Polycythaemia vera (PV) patients were younger than those with secondary polycythaemia. PV was found mainly to affect males.
2. Risk for thrombosis in both types of polycythaemia increases with age and with increasing PCV level.
3. All cases of secondary polycythaemia were due to either chronic lung disease or congenital heart disease with low arterial oxygen saturation.
4. Thrombocytosis and leucocytosis were the main haematological abnormalities in PV. Basophilia was not seen in all cases, PT and APTT were normal in all cases.
5. Hyperuricaemia was more frequent among patients with PCV levels equal or above 0.54L/L.
6. Venesection was the best method for treatment in both groups of polycythaemia.
7. We have established an equation when applied to patients with polycythaemia can predict PCV reduction values after donating a given number of blood units.

**References**

Trauma; frequency of missed intra-abdominal injuries in Al-Sulaimaniyah Teaching Hospital/ Emergency Department

Hiwa O. Ahmed*, Salam Nizam Aldeen Shams Aldeen**

* Department of Surgery, Medical College, University of Al-Sulaimaneyah, Al-Sulaimaneyah City; ** General Surgeon, Sulaimaniyah Teaching Hospital.

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ABSTRACT

Background: The most common reason for injuries to be missed is altered level of consciousness due to head injury or alcohol. Other reasons include severity of injury and instability requiring immediate operation, lack of symptoms at admission, technical problems, and low index of suspicion by the examiner. Missed injuries can occur at any stage of the management of patients with major trauma. Any delay in providing the necessary treatment may lead to increased morbidity and mortality.

Objective: To find the frequency of missed intra-abdominal injuries and their mortality, to raise suspicion of potential missed injuries in order to avoid these preventable deaths.

Methods: A retrospective study including 2978 patients with abdominal injuries out of 13201 traumatized patients in 2006. Records were reviewed for demographics, injury characteristics, and associated injuries, missed injuries, need and indications of reoperation, morbidity and mortality.

Results: The study included 2978 trauma victims; 2195 males and 783 females, with a male to female ratio of about 4:1. Their age ranged from 2-87 years, median age 39.5 and peak age of trauma was 31 years. From 2978 patients with abdominal injuries, there were 28 deaths (1.06%), and four missed injuries (0.134%).

Conclusion: A careful history taking, precise and repeated clinical examinations, complete diagnostic procedures, complete surgical explorations, and proper timing of reoperation are necessary for patients with blunt abdominal injuries, which are cornerstones in improving the quality of trauma care.

Keywords: Trauma patient, missed injuries, missed abdominal injuries, small intestinal injuries, and preventable death.
Increased number of emergency admissions, unstable patients, incomplete histories, time-critical decisions, concurrent tasks, involvement of many disciplines and often junior personnel working after-hours in busy emergency departments create a perfect storm for medical errors. (1,2) One of these avoidable errors is missed intra-abdominal injuries (MIAI), which could be defined as “unsuspected intra-abdominal injury requiring laparotomy in patients otherwise undergoing non operative management (NOM)” (3). It is clear that missed injuries adversely affect patients outcomes and damage physicians/institutional credibility (4) which could be avoided by “The timely treatment of the injury continues to rely on a high index of clinical suspicion and serial examinations by an experienced surgeon” (5). The most common reason for injuries to be missed is altered level of consciousness due to head injury or alcohol. Other reasons include severity of injury and instability requiring immediate operation, lack of symptoms at admission, technical problems, and low index of suspicion by the examiner. (3, 6) Missed injuries can occur at any stage of the management of patients with major trauma, any delay in providing the treatment necessary may lead to increased morbidity and mortality. (7) In many literatures the incidence of missed injuries is significant (8.1%) (6, 7). Understanding the etiology of missed injuries is essential in minimizing its occurrence. (6) Among these injuries blunt abdominal trauma needs early and prompt identification and it can be challenging, and failure to detect these injuries initially can lead to preventable complications. (8).

Autopsies are useful in uncovering missed injuries or undiagnosed conditions that contribute to death after injury (9), otherwise valuable information regarding possible missed injuries and potential improvements in management will be lost (10).

Our aim is to find the frequency of the missed intra-abdominal injuries and their mortality, to raise the index of suspicion of potential missed injuries in order to avoid these preventable deaths, and improve the quality of the emergency medical services.

Methods

A retrospective study including 2978 patients with abdominal injuries from the sum of 13201 traumatized patients in the 2006. Most of these patients were received directly after an accident from Al Sulaimaniyah city center or nearby areas which are served by Al-Sulaimaniyah Teaching Hospital/ a tertiary hospital in Iraqi Kurdistan Region, receiving annually over 20000 surgical emergencies. As recorded in the files; the initial examination was carried out by the trauma team in the Emergency Department (ED) according to standard protocols. Resuscitation was carried out according to Advanced Trauma Life Support principles. Patients were later reexamined as frequently as needed. Records were reviewed for demographics, injury characteristics, associated injuries, missed injuries, need and indications of reoperation, morbidity and mortality. Postmortem results of the 122 deceased patients were taken from Al Sulaimaniyah Forensic Institute; medical records of another 12 deaths were missing, who were excluded from the study. The study was approved by the Ethics Committee of the University of Al Sulaimaniyah-College of Medicine. All the data were analyzed by SPSS (statistical package for social science) version 16. Qui square analysis was done, P value less than 0.05 was considered positive and statistically important.
Results
The study included 2978 abdominal trauma victims; 2195 males and 783 females, with a male to female ratio of about 4:1. Their age ranged from 2- 87 years, median age 39.5 and peak age of trauma was 31 years. Three quarters of the injuries were caused by blunt trauma, road traffic accidents being the commonest (61.8%), and then falls (14.9%). While in the penetrating injuries gunshot injuries (13.9%) were the most frequent penetrating type. Mortality was 1.1 % (134 patients, 12 exclude because of missing of their medical records). About two third of deaths had sustained head injury (77.9%), only 28 deaths had abdominal injuries and many victims had multiple injuries (Table1).

From 2978 patients with abdominal injuries (Table 2), there were 28 deaths (1.06%), and four missed injuries (0.13%). Three missed injuries were intraoperative. One who had laparotomy for severely injured liver with severe haemoperitonium, and 49 hours later on reoperation, revealed shattered right kidney. The other two patients had undergone laparotomy for spleen avulsion and deep laceration in the spleen, while small intestine injuries were missed, revealed 4 days later during reoperation. The fourth one had multiple injuries by a heavy blunt object and was treated for the thoracic and orthopedic injuries while abdominal injury in the form of duodenal damage was missed, and died on the 5th posttrauma day. Postmortem revealed missed posterior duodenal tear and periduodenal bilious debris and pus collection (Table 3).

We could notice that three quarters of the missed injuries (Table 4), were intestinal lacerations and occurred in the patients who sustained blunt abdominal injuries. Injuries were missed in two of the patients in the first operation, and the third diagnosed at autopsy.

Table 1: The frequencies of injuries in anatomical body regions.

<table>
<thead>
<tr>
<th>Injured Region</th>
<th>No.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Head</td>
<td>95</td>
<td>77.9</td>
</tr>
<tr>
<td>Multiple superficial wounds</td>
<td>42</td>
<td>34.4</td>
</tr>
<tr>
<td>Lower limb fractures</td>
<td>28</td>
<td>23</td>
</tr>
<tr>
<td>Chest</td>
<td>21</td>
<td>17.2</td>
</tr>
<tr>
<td>Abdomen, pelvis</td>
<td>28</td>
<td>23</td>
</tr>
<tr>
<td>Spine</td>
<td>7</td>
<td>5.7</td>
</tr>
</tbody>
</table>

* Some patients injured in more than one anatomical region.

Table (2): Details of the intra-abdominal injuries.

<table>
<thead>
<tr>
<th>Injured organs</th>
<th>No. and %</th>
<th>Operated on</th>
<th>Non-operative management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal wall</td>
<td>804 (26.99%)</td>
<td>393</td>
<td>407</td>
</tr>
<tr>
<td>Small intestine</td>
<td>435 (14.60%)</td>
<td>433</td>
<td>2</td>
</tr>
<tr>
<td>Pelvic # with bladder and or urethra</td>
<td>370 (12.42%)</td>
<td>370</td>
<td>0</td>
</tr>
<tr>
<td>Liver, spleen</td>
<td>326 (10.94%)</td>
<td>326</td>
<td>0</td>
</tr>
<tr>
<td>Kidneys and ureter</td>
<td>132 (4.43%)</td>
<td>18</td>
<td>114</td>
</tr>
<tr>
<td>Large intestine</td>
<td>111 (3.72%)</td>
<td>111</td>
<td>0</td>
</tr>
<tr>
<td>Combined (Polytrauma)</td>
<td>800 (26.86%)</td>
<td>369</td>
<td>431</td>
</tr>
<tr>
<td>Total</td>
<td>2978 (100%)</td>
<td>1894</td>
<td>1084</td>
</tr>
</tbody>
</table>
Table (3): Details of the missed intra-abdominal injuries in four patients.

<table>
<thead>
<tr>
<th>Stage of ATLS</th>
<th>Missed intra-abdominal injury</th>
<th>Survived No. and %</th>
<th>Died No. and %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tertiary Assessment</td>
<td>Duodenal tear</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Intra-operative</td>
<td>Renal injury</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Small intestine</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>4</td>
<td>2</td>
</tr>
</tbody>
</table>

Table (4): Details of the intestinal injuries.

<table>
<thead>
<tr>
<th>Condition of the intestinal injury (Small and large)</th>
<th>Type of the injury</th>
<th>Missed injury</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Penetrating</td>
<td>Blunt</td>
<td></td>
</tr>
<tr>
<td></td>
<td>HVM*</td>
<td>SW**</td>
<td></td>
</tr>
<tr>
<td>single</td>
<td>46</td>
<td>37</td>
<td>463</td>
</tr>
<tr>
<td>Combined with intra-abdominal injuries</td>
<td>39</td>
<td>10</td>
<td>90</td>
</tr>
<tr>
<td>Combined with extra-abdominal injuries</td>
<td>2</td>
<td>1</td>
<td>32</td>
</tr>
</tbody>
</table>

* HVM: High velocity missiles.
** SW: Stab wound.
P value less than 0.05 considered significant.

**Discussion**

Missed injuries still occur at an unacceptably high rate in trauma patients (11), it is mentioned in details in the literature and the incidence is (8.1-22%) (6,7,11). But incidence of missed intra-abdominal injuries (3-18%) is mentioned less in the literature (12), claiming that it will not result in mortality, although it’s associated with significant morbidity (5,13). While others found 0.19% of necessary reoperation and (0.29%) mortality in patients with missed injuries. In the results of the current work need for reoperation was 0.1% which is comparable to the literature (14) and mortality was (1.1%) with (p value 0.0317).

Missed intestinal lacerations may be difficult to diagnose. There may be no initial or typical clinical presentation of the abdominal injuries especially in patients with multiple injuries or when there is change in the consciousness of the victim, even after examination with ultrasonography and CT scan of the abdomen and pelvis (5,11,12), it is still not easy. Ultimately, the decision for exploratory laparotomy should be a clinical decision (5,13,15) and high index of clinical suspicion helps in the recognition of these types of injuries (12). The timely treatment of these injuries continues to rely on a high index of clinical suspicion and serial examinations by an experienced surgeon (5), which may help in improving the quality of trauma care (11).

Although in initial assessment, one still has to treat the greatest threat on life before complete diagnosis of all injuries, but alertness to evolving injuries must remain throughout the patient’s stay in the hospital (7). Acute physiological derangements can occur at any time after the original injury, with life threatening sequelae (16).

The majority of treatment errors occur in the emergency department, the intensive care unit (ICU) and the operating room (11). The results of this work revealed 4 missed intra-abdominal injuries (MIAI) (Table 3), one missed in the ED, ICU and there was no suspicion of the injury (duodenal lacerations) before death. Other three cases were missed in the ED, ICU and in the first operation (2 patients with small intestinal lacerations and one with shuttered right kidney).

The presence of associated intra-abdominal injuries significantly affected the presentation and time of diagnosis of patients with small...
bowel injuries (SBI)\(^{12}\) and any delay in the surgical treatment in trauma victims over 90 min increases mortality of 1 % every 3 minutes\(^{17,18}\). Patients inflicted with more severe associated injuries were less likely to survive the trauma\(^{12}\).

**Conclusion**

A careful history taking, precise and repeated clinical examinations, complete diagnostic procedure, complete surgical explorations, and timing early reoperation are necessary for patients with blunt abdominal injuries, which are cornerstones in improving the quality of trauma care.

**Acknowledgements**

We would like to thank all the doctors on duty in Al Sulaimaniyah Casualty Hospital; paramedical workers for their technical support, and we also thanks Dr. Fatah Hawramani for his statistical analysis of the results.

**References**

Quality of life of patients with type 2 diabetes mellitus in Mosul

Wafaa Abdul Aziz Mostafa*, Mohammad Yousif Almkhtar**

* M.sc. Candidate, **Department of Community Medicine, College of Medicine, University of Mosul.

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ABSTRACT

Background: Prevalence of diabetes mellitus is increasing in developed and developing countries. Diabetes is known to strongly affect the health-related quality of life (HRQOL).

Objectives: To assess the quality of life of patients with type 2 diabetes mellitus and to determine the clinical and sociodemographic factors that affect the quality of life of these patients.

Patients and methods: This was a case series health center based study, the data for this research was taken from an MSc research during the data collection phase. A 300 patients with type 2 diabetes mellitus attending AL-Wafaa Diabetic Centre in Mosul. The world health Organizations quality of life assessment (WHOQOL-BREF), short version questionnaire was applied to assess quality of life after being modified and translated to local Arabic language.

Results: The overall QOL show that most of the respondents performed fairly well on the questionnaire used, 41% had good score, 46% had fair score and 13% had poor score. For physical activity domain 30% had poor score, for social domain 14% had poor score, for psychological and envirornmental domains 23% had poor score.

Conclusion: This study supports previous reports that QOL of patients with diabetes mellitus was fairly good and D.M significantly affects physical health especially in females. Further community based cross sectional studies is recommended for measuring QOL in DM.

Keywords: Type 2 diabetes mellitus, quality of life.
Diabetes mellitus is one of the chronic non-communicable diseases that is plaguing both developed and developing countries at an alarming rate. It has reached epidemic proportion. According to World Health Organization (WHO): there is an apparent epidemic of diabetes which is strongly related to economic and life style changes. It is now vastly visible as a growing health problem in developing economies as almost 80% of diabetes deaths occur in low and middle income countries. In Iraq, according to the national chronic non-communicable diseases risk factor survey done in 2006, the prevalence of DM is 10.4%.

Diabetes mellitus is a demanding disease that affects a person's health-related quality of life, a person's ability to function, they have to eat carefully, exercise, test their blood glucose and based on the result decide when to schedule their next meal or medication.

Quality of life (QOL): is of central concern in evaluative research and improved quality of life is probably the most desired outcome of all healthcare policies. QOL has been defined as a “descriptive term that refers to people's emotional, social and physical well being and their ability to function in the ordinary tasks of living”. Health related quality of life (HRQOL), on the other hand, includes domains (aspects) of life that improve when a treatment option is successful. A clinically significant change in HRQOL is indicated by a decline in a domain that leads a physician or health care provider to alter a medication or medical treatment. HRQOL domains minimally include physical state, mental health or emotional wellbeing. These domains represent typical outcomes in medical and social science research. Numerous studies have been done to evaluate the effect of DM on the sufferer’s QOL in the developed world.

We aim to assess the QOL of our patients with T2DM and to determine the clinical and socio-demographical factors that affect the QOL of these patients.

Patients and methods
Approval of study proposal has been obtained through a seminar at the Community Medicine Department. Therefore essential official permissions have been obtained from Nineveh Health Office to conduct this study.

Settings
The study was done in AL-Wafaa Diabetic Center during the period spanning from September 2010 to March 2011. The data in this study was a part of MSc research done in this centre. This centre is attached to Ibn – Sena Teaching Hospital at the West side of Mosul City – North of IRAQ which has been established in 1999.

This is a case-series study, the patients were aged twenty years and above of both sexes; all patients had T2DM diagnosed by the consultant endocrinologist; DM of the young (less than 20 years), gestational DM and duration since diagnosis less than 1 year are excluded from this study. The patients were interviewed by the researcher after being informed and consent of patients were obtained.

Questionnaire
The instrument used is the World Health Organization quality of life questionnaire-short version (WHOQOL-BREEF) which is a generic instrument with cross-cultural application and has been used as a measure of HRQOL for chronic medical illnesses in many researches in the Middle East and Asian countries. This questionnaire is modified, translated and approved by the staff of Community Medicine department of College of Medicine, University of Mosul to fit with local tradition and language (Appendix). The WHOQOL-BREEF contains four specific domains which include: physical health, psychological well being, social relationships and environmental condition.

Some limited socio-demographics characteristics (e.g. age, sex, marital status, educational level) and disease related information (e.g. duration of diabetes, family history of diabetes) were also considered.

Scores were used for each question, then the median score calculated in the four domains.
the scores of items within each domain are used to calculate domain scores. A score of mean ± 1 standard deviation (SD) on each domain is graded ‘fair’, a score of < mean - 1 SD is ‘poor’, and a score of > mean + 1 SD is good (15).

**Statistical analysis**

Data collected were entered into Microsoft excel and loaded into the Statistical Package for Social Sciences (SPSS) software (version 16 Chicago IL USA) for descriptive statistical analyses.

**Results**

Three hundreds consecutive attendees of the diabetes clinic met the inclusion criteria during the course of the study; 169 were females and 131 were males. For overall QOL, 123 (41%) had good score, 138 (46%) had a fair score and 39 (13%) had poor score, Table (1).

Those patients with mean age of (51.23) years had good score, while those with mean age of (54.34) had fair score and patients with poor score had mean age of (55.97), Table (2).

The QOL in both physical and psychological domain were inversely related to increasing age of the patients. Regarding duration of illness, those patients with mean duration of (8.86) years had poor score while those of good score mainly had a mean of (6.65) years, Table (3).

The QOL score is high in all the domains except in environmental domain at which the majority of patients had fair to poor score and only (38) patients had good score, in the four domains the QOL score is higher in males than in females, for example, in physical health domain more than half (79) patients from (126) patients who had good score were males and the remaining were females, Table (4).

### Table (1): Relationship between qualities of life outcomes and sociodemographic variables.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Overall quality of life</th>
<th></th>
<th></th>
<th></th>
<th>Total No. %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Good</td>
<td>Fair</td>
<td>Poor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>123</td>
<td>138</td>
<td>39</td>
<td></td>
<td>300</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>46</td>
<td>92</td>
<td>31</td>
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<td>169</td>
</tr>
<tr>
<td>Male</td>
<td>77</td>
<td>46</td>
<td>8</td>
<td></td>
<td>131</td>
</tr>
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<td></td>
<td></td>
</tr>
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<td>1</td>
<td>1</td>
<td></td>
<td>3</td>
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<tr>
<td>Married</td>
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<td>107</td>
<td>21</td>
<td></td>
<td>239</td>
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<tr>
<td>Widowed</td>
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<td>28</td>
<td>17</td>
<td></td>
<td>54</td>
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<tr>
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### Table (2): Quality of life and patients’ characteristics.

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<th></th>
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<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Good</td>
<td>Fair</td>
<td>Poor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean Age (SD) [Years]*</td>
<td>51.234</td>
<td>54.435</td>
<td>55.795</td>
<td></td>
<td>100%</td>
</tr>
<tr>
<td></td>
<td>(9.199)</td>
<td>(7.797)</td>
<td>(7.164)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean Duration of Illness (SD) [Years]**</td>
<td>6.309</td>
<td>7.449</td>
<td>9.769</td>
<td></td>
<td>100%</td>
</tr>
<tr>
<td></td>
<td>(5.105)</td>
<td>(5.588)</td>
<td>(7.143)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Family History of Diabetes Mellitus***</td>
<td>123</td>
<td>138</td>
<td>39</td>
<td></td>
<td>100%</td>
</tr>
<tr>
<td>Yes (1)</td>
<td>88</td>
<td>113</td>
<td>33</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No (2)</td>
<td>35</td>
<td>25</td>
<td>6</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*P<0.05  **P<0.05  ***P<0.05.
Table (3): Quality of life and patients' characteristics according to domains.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Domain 1</th>
<th></th>
<th>Domain 2</th>
<th></th>
<th>Domain 3</th>
<th></th>
<th>Domain 4</th>
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<tbody>
<tr>
<td></td>
<td>Good</td>
<td>Fair</td>
<td>Poor</td>
<td>Good</td>
<td>Fair</td>
<td>Poor</td>
<td>Good</td>
<td>Fair</td>
</tr>
<tr>
<td>Mean Age (SD) [Years]</td>
<td>49.169</td>
<td>(8.822)</td>
<td>55.762</td>
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<td>56.156</td>
<td>(6.876)</td>
<td>51.070</td>
<td>(8.421)</td>
</tr>
<tr>
<td>Mean Duration of Illness (SD) [Years]</td>
<td>6.659</td>
<td>(5.229)</td>
<td>6.524</td>
<td>(5.217)</td>
<td>8.867</td>
<td>(6.401)</td>
<td>6.556</td>
<td>(5.338)</td>
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<td>84</td>
<td>90</td>
<td></td>
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<td>129</td>
<td>102</td>
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<tr>
<td></td>
<td>No</td>
<td>27</td>
<td>23</td>
<td>16</td>
<td>29</td>
<td>80</td>
<td>54</td>
<td>119</td>
</tr>
</tbody>
</table>

Table (4): Relationship between quality of life outcomes and sociodemographic variables according to domains.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Domain 1</th>
<th></th>
<th>Domain 2</th>
<th></th>
<th>Domain 3</th>
<th></th>
<th>Domain 4</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Good</td>
<td>Fair</td>
<td>Poor</td>
<td>Good</td>
<td>Fair</td>
<td>Poor</td>
<td>Good</td>
<td>Fair</td>
</tr>
<tr>
<td>Sex</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>126</td>
<td>84</td>
<td>90</td>
<td>129</td>
<td>102</td>
<td>69</td>
<td>158</td>
<td>100</td>
</tr>
<tr>
<td>Male</td>
<td>47</td>
<td>50</td>
<td>72</td>
<td>53</td>
<td>62</td>
<td>54</td>
<td>74</td>
<td>60</td>
</tr>
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<td>Marital Status</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single</td>
<td>126</td>
<td>84</td>
<td>90</td>
<td>129</td>
<td>102</td>
<td>69</td>
<td>158</td>
<td>100</td>
</tr>
<tr>
<td>Married</td>
<td>116</td>
<td>63</td>
<td>60</td>
<td>114</td>
<td>81</td>
<td>44</td>
<td>137</td>
<td>73</td>
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<tr>
<td>Widowed</td>
<td>7</td>
<td>19</td>
<td>28</td>
<td>11</td>
<td>19</td>
<td>24</td>
<td>19</td>
<td>22</td>
</tr>
<tr>
<td>Divorced</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>3</td>
</tr>
</tbody>
</table>

Discussion
The present study found that the overall perception of (HRQOL) of patients with DM was actually affected by the disease. The result of a previous study showed that patients with DM experienced a good QOL in comparison to other chronic disease groups and even to healthy population and the majority of patients with T2DM experience a high degree of well-being, satisfaction and enjoyment (15).

In this study it was seen that there is a decrease in HRQOL with increasing mean age of the patients; this is similar to the result of a study in Saudi Arabia (13). There is a clearly visible effect of gender on QOL; female patients had low score in QOL compared to males. This may be due to the high prevalence of obesity in female patients in our locality, this result is similar to other studies (13,15-17). Regarding to duration of illness, poor QOL is related to high mean of duration of illness; this is likely due to the appearance of complications with time. A study in Saudi Arabia showed that the duration of illness had no significant effect on QOL (13), while Swedish bases population study which reported that the duration of disease significantly correlate with QOL, and notice that subject with duration more than 5 years had better QOL (18). This may be due to good control and adaptation of the patients with diabetic life style. Another study in Kuwait (16) showed that the duration of illness had a significant impact only on the environmental domain.
The social domain which assesses personal relationships showed a high mean score in (HRQOL) of our patients; this probably is due to a very large extent to high degree of satisfaction to the items of this domain. This finding however was similar to a previous study by Awadalla et al (16) who reported no difference in the score of patients with diabetes in relation to general population on the social relationships domain. It is worthy of note that Awadalla et al patients had a good level of social support and had strong family care giver support system. It has been shown that the family is a major source of support reflecting better psychological adjustment of the patient to the disease (16).

In respect to environment domain this research demonstrated that the majority of patients got fair score. This does not agree with other studies (17,19), which revealed that: the score of the environment domain was much lower than the other three domains and this could be due to bad environmental condition in these localities.

The major limitations of this study are the health center based sample in that it may not be representative of patients with diabetes mellitus throughout Mosul, although it is the main center in the city. As there are no previous studies on QOL of patients with diabetes mellitus using the (WHOQOL-BREF) in IRAQ, direct comparison with other studies is difficult.

Conclusion
This study supports previous reports that QOL of patients with diabetes mellitus was fairly good and D.M significantly affects physical health especially in females. Further community based cross sectional studies is recommended for measuring QOL in DM.

References

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Appendix

Study questionnaire form

Serial number  Name   Age:
Sex:    male      female
Marital state:  single    married     widowed     divorced
Family history of diabetes:  yes     no
Duration of illness:(    ) years

Quality of life questionnaire

A-Physical health:
1-Energy and fatigue.
2-Pain and discomfort.
3-Sleep and rest.
4-Activity on daily living.
5-Mobility.
6-Depend on medical.
7-Work capacity.

B- Psychological health
1-Bodily image and appearance.
2-Negative feeling.
3- Positive feeling.
4-Self esteem.
5-Thinking, learning, memory and concentration.

C-Social relationship
1-Personal relation.
2-Social support.

D-Environmental state
1-Financial resources.
2-Freedom, physical safety and security.
3-Health and social care.
4-Home environment.
5-Opportunities for acquiring new information and skills.
6-Participation and opportunities for recreation and leisure.
7-Physical environment (noise, pollution, climate).
8-Transport.
Diabetes mellitus and lung function tests

Dhaher J. S. Al-Habbo*, Afraa M. Al-Ameen**

* Department of Medicine;** Department of Physiology, College of Medicine, University of Mosul.

Received: 20th Mar. 2011; Accepted: 26th Oct. 2011.

ABSTRACT

Objective: To measure the effects of type 1 and type 2 diabetes mellitus on the various spirometric pulmonary function tests

Methods: This study involved 70 diabetic patients, 25 type 1 and 45 type 2 diabetes mellitus, and 45 control group. Type 1 diabetic patients included 14 males and 11 females, their ages ranging from 17-63 years with their mean was 47.12, with SD12.83. Type 2 diabetic patients included 26 males and 19 females; their ages ranging from 19-63 years with their mean 46.67, with SD 9.50. The control group involved 24 males and 21 females, their ages ranging from 13-68 years with their mean 38.78, with SD13.3.

The study was conducted in Ibn Sena Teaching Hospital - Medical Outpatient Clinic, Al-wafa Medical Center in Mosul, and Mosul University-Medical Center.

Results: There were statistically significant differences between the control group and type 1 diabetes mellitus during the measurements of FVC%, FEV1/FVC% and MMFR%, with statistically significant reductions in their values when compared to controls. Furthermore, type 2 diabetes mellitus has significant effects on FVC%, FEV1 and FEV1/FVC% when compared with the controls, with statistically significant differences from the control group. There were no much differences between them apart from the FVC% which favors type 1 diabetes mellitus over type 2 diabetes mellitus with highly significant P-value.

Conclusion: The present study clearly indicates that both type 1 and type 2 diabetes mellitus adversely affects the various pulmonary function tests, and the results are in accord with other previous studies.

Keywords: Spirometry, diabetes mellitus various types.
The lung can be considered as one of the end organs which can be adversely affected by diabetes; reduced lung function may occasionally be present even before the clinical recognition of diabetes although it will not be the presenting symptom\(^1\), suggesting that the lung may be involved in the pathogenesis of diabetes.

There is growing evidence which supports the association between reduced lung function and diabetes \(^2\). The improvements in lung function following intensive insulin therapy \(^3\) support the concept that the lung may be a target organ for damage in diabetes.

Diabetes has been associated with asthma at the population level \(^4\), suggesting that despite their immunological differences, susceptibility to diabetes and asthma may be influenced by common environmental factors.

The large size alveolar-capillary network is protected against gross respiratory complications at a given level of systemic microvascular destruction. Therefore lung function tests could provide useful measures to follow the progress of systemic microangiopathy in diabetics. \(^5\)

In diabetic patients forced expiratory volume in the first second (FEV1) declines at twice the physiological rate regardless of the presence of documented autonomic neuropathy. \(^6\)

Patients with diabetes without a smoking history or clinical lung disease consistently demonstrate a modest restrictive ventilator defect with proportional (8–20%) reductions in lung volume, forced vital capacity (FVC), FEV1, and forced expiratory flow in the midrange of vital capacity compared to subjects without diabetes \(^7\) and in relation to glycemic control. \(^8\) Total lung capacity, lung elastic recoil, and dynamic lung compliance were abnormally reduced in type 1 diabetes. \(^9\)

The aims of this study are to measure the effects of type 1 and type 2 diabetes mellitus on the various spirometric tests and also to study the effect of the duration of diabetes mellitus, the age and sex of the patient on these various tests.

**Patients and methods**

This study involved 70 diabetic patients 25 type 1 and 45 type 2 diabetes mellitus, and 45 control group. Type 1 diabetic patients included 14 men and 11 women, their ages ranging from 17-63 years with their mean 47.12 with SD 12.83. Type 2 diabetic patients included 26 men and 19 women; their ages ranging from 19-63 years with their mean 46.67 and with SD 9.50. The control group involved 24 men and 21 women, their ages ranging from 13-68 years with their mean 38.78 with SD13.3.

The exclusion criteria were as follows: Patients with known history of acute or chronic respiratory infections which may interfere with lung function tests, neuromuscular disease, cardiopulmonary disease and those who had undergone chest surgery or other major operations. Subjects with history of smoking and patients with gross abnormalities of the thoracic cage which may interfere with lung function test were also excluded from the study. Furthermore patients with overt diabetic neuropathy, retinopathy and nephropathy were also excluded from the study.

All the spirometric measurements were carried out in the outpatient department of Ibn-Sena Teaching Hospital during the early morning, while the subjects were in standing position. All the measurements were done by
using DISCOM 14 Spirometer (Germany). Most patients were referred from Al-wafa Medical Center in Mosul, and the private clinics of the authors.

The following pulmonary function tests were carried out for the patients and the controls: Forced Vital Capacity (FVC), Forced Expiratory Volume in first second (FEV1), Forced Expiratory Ratio (FEV1/FVC), Forced Expiratory Flow (FEF25-75% MMFR) and Peak Expiratory Flow (PEF), with calculation of their percentage of predictive values.

**Statistical analysis**

The various lung function tests were reported in absolute volume as well as the per cent of their predicted values, the percent of predicted values were mostly used in the statistical analysis. After calculation of the mean and the standard deviation, the statistical analysis was conducted using unpaired T-test to compare the lung function tests values in type 1 and type 2 diabetes mellitus with the control group. The level of significance was taken as p<0.025.

**Results**

To study the effects of diabetes mellitus on the various lung function tests, we compared the effects of type 1 diabetes mellitus on the lung function tests by comparing it with the control group as in table (1).

There were statistically significant differences between the control group and type 1 diabetes mellitus during the measurements of FVC%, FEV1/FVC% and MMFR%, with statistically significant reductions in their values when compared with the controls. These results prove that type 1 diabetes mellitus patients have significant effects on the various lung function tests as restrictive pulmonary defect and even obstructive ventilator defect.

Furthermore, we compared the effects of type 2 diabetes mellitus on the lung function tests by comparing it with the control group as in table (2).

These results asserting that type 2 diabetes mellitus has significant effects on many lung function tests as compared with the controls, especially during the measurements of FVC%, FEV1 and FEV1/FVC% with statistically significant differences between the control group and type 2 diabetes mellitus, with statistically significant reductions in the value of these tests when we compare them with the control group. All these result go with restrictive pulmonary defect.

To determine the difference between type 1 and type 2 diabetes mellitus and their effects on the various lung function tests, we studied the differences between them as in table (3) by using unpaired T-test, this type of study indicates that there were no much differences between them apart from the FVC% which favors type 1 diabetes mellitus over type 2 diabetes mellitus with highly significant P-value as shown below in table (3). This test indicates that type 1 and type 2 diabetes mellitus have similar effect on the various lung function tests.

The duration of diabetes in the two groups seems to have no significant effects on the lung function tests values, as most of the patients in the sample studied had their diabetes mellitus duration less than 10 years, apart from 5 patients in type 1 and 5 patients in type 2 diabetes mellitus as seen in table (4).

<table>
<thead>
<tr>
<th>Type</th>
<th>Test type % of predictive value</th>
<th>Number of patients</th>
<th>Mean</th>
<th>SD</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 1 Diabetes</td>
<td>FVC%</td>
<td>45</td>
<td>79.7</td>
<td>15.9</td>
<td>0.001</td>
</tr>
<tr>
<td>Control Group</td>
<td></td>
<td></td>
<td>90.5</td>
<td>10.3</td>
<td></td>
</tr>
<tr>
<td>Type 1 Diabetes</td>
<td>FEV1%</td>
<td>45</td>
<td>88.5</td>
<td>6.7</td>
<td>0.714 (N)</td>
</tr>
<tr>
<td>Control Group</td>
<td></td>
<td></td>
<td>87.9</td>
<td>5.8</td>
<td></td>
</tr>
<tr>
<td>Type 1 Diabetes</td>
<td>FEV1/FVC%</td>
<td>45</td>
<td>71.6</td>
<td>13.9</td>
<td>0.000</td>
</tr>
<tr>
<td>Control Group</td>
<td></td>
<td></td>
<td>84.4</td>
<td>8.9</td>
<td></td>
</tr>
<tr>
<td>Type 1 Diabetes</td>
<td>MMFR%</td>
<td>45</td>
<td>87.2</td>
<td>20.5</td>
<td>0.014</td>
</tr>
<tr>
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<td></td>
<td>97.8</td>
<td>14.5</td>
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</tr>
<tr>
<td>Type 1 Diabetes</td>
<td>PEFR%</td>
<td>45</td>
<td>84.5</td>
<td>12.4</td>
<td>0.265 (N)</td>
</tr>
<tr>
<td>Control Group</td>
<td></td>
<td></td>
<td>87.6</td>
<td>10.8</td>
<td></td>
</tr>
</tbody>
</table>
Table (2): Comparison the lung function in type 2 diabetes mellitus and controls.

<table>
<thead>
<tr>
<th>Type</th>
<th>Test type % of predictive value</th>
<th>Number of patients</th>
<th>Mean</th>
<th>SD</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 2 Diabetes</td>
<td>FVC%</td>
<td>45 45</td>
<td>95.0</td>
<td>13.5</td>
<td>0.077</td>
</tr>
<tr>
<td>Control Group</td>
<td></td>
<td></td>
<td>90.5</td>
<td>10.3</td>
<td></td>
</tr>
<tr>
<td>FEV1%</td>
<td>45 45</td>
<td>84.4</td>
<td>8.7</td>
<td>18.7</td>
<td>0.027</td>
</tr>
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<td></td>
<td>100.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEV1/FVC%</td>
<td>45 45</td>
<td>76.3</td>
<td>7.2</td>
<td>8.9</td>
<td>0.000</td>
</tr>
<tr>
<td>Control Group</td>
<td></td>
<td></td>
<td>84.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MMFR%</td>
<td>45 45</td>
<td>95.1</td>
<td>24.5</td>
<td>14.5</td>
<td>0.385 (N)</td>
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<td></td>
<td>97.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PEFR%</td>
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<td>88.4</td>
<td>11.9</td>
<td>10.8</td>
<td>0.775 (N)</td>
</tr>
</tbody>
</table>

Table (3): Comparison the lung function in type 1 and type 2 diabetes mellitus.

<table>
<thead>
<tr>
<th>Type</th>
<th>Test type % of predictive value</th>
<th>Number of patients</th>
<th>Mean</th>
<th>SD</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 1 Diabetes</td>
<td>FVC%</td>
<td>25 45</td>
<td>79.7</td>
<td>15.9</td>
<td>0.000</td>
</tr>
<tr>
<td>Type 2 Diabetes</td>
<td></td>
<td></td>
<td>95.00</td>
<td>13.5</td>
<td></td>
</tr>
<tr>
<td>FEV1%</td>
<td>25 45</td>
<td>88.5</td>
<td>6.7</td>
<td>8.7</td>
<td>0.063 (N)</td>
</tr>
<tr>
<td>Type 1 Diabetes</td>
<td></td>
<td></td>
<td>84.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type 2 Diabetes</td>
<td>FEV1/FVC%</td>
<td>25 45</td>
<td>71.6</td>
<td>13.9</td>
<td>0.062 (N)</td>
</tr>
<tr>
<td>Type 1 Diabetes</td>
<td></td>
<td></td>
<td>76.3</td>
<td>7.20</td>
<td></td>
</tr>
<tr>
<td>Type 2 Diabetes</td>
<td>MMFR%</td>
<td>25 45</td>
<td>87.2</td>
<td>20.5</td>
<td>0.234 (N)</td>
</tr>
<tr>
<td>Type 1 Diabetes</td>
<td></td>
<td></td>
<td>94.1</td>
<td>24.5</td>
<td></td>
</tr>
<tr>
<td>Type 2 Diabetes</td>
<td>PEFR%</td>
<td>25 45</td>
<td>84.5</td>
<td>12.4</td>
<td>0.201 (N)</td>
</tr>
<tr>
<td>Type 1 Diabetes</td>
<td></td>
<td></td>
<td>88.4</td>
<td>11.9</td>
<td></td>
</tr>
<tr>
<td>Type 2 Diabetes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table (4): The effects of duration of diabetes mellitus on the lung function tests.

<table>
<thead>
<tr>
<th>Mean Type 1 DM</th>
<th>Mean Type 2 DM</th>
<th>SD Type 1</th>
<th>SD Type 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVC%</td>
<td>79.7</td>
<td>95</td>
<td>15.9</td>
</tr>
<tr>
<td>FEV1%</td>
<td>88.5</td>
<td>84.4</td>
<td>6.7</td>
</tr>
<tr>
<td>FEV1/FVC%</td>
<td>71.6</td>
<td>76.3</td>
<td>13.9</td>
</tr>
<tr>
<td>MMFR%</td>
<td>87.0</td>
<td>94</td>
<td>20.6</td>
</tr>
<tr>
<td>PEFR%</td>
<td>84.6</td>
<td>88.4</td>
<td>12.4</td>
</tr>
<tr>
<td>Duration</td>
<td>5.5</td>
<td>6.7</td>
<td>4.0</td>
</tr>
<tr>
<td>Number of patients</td>
<td>25</td>
<td>45</td>
<td></td>
</tr>
</tbody>
</table>

Discussion
Pulmonary indices are largely independent of physical fitness and the secondary sequel of diabetic end-organ failure usually does not interfere with the interpretation of the various lung function tests (10). Therefore this study
depends on spirometric measurement to assess the effect of diabetes mellitus on lung function test.

Williams JG and others since 1984 demonstrated that more than one third of patients with diabetes showed abnormal ventilator response to exercise, hypercapnia, or hypoxia consistent with autonomic neuropathy. (5)

The present study demonstrates that type 1 diabetes mellitus has significant effects on the lung function tests during the measurements of FVC%, FEV1/FVC% and MMFR%, with statistically significant reductions in their values when compared with the controls, but FEV1% and PEFR% were more or less the same as the control group. These results are consistent with the findings by Sandler M and others (11). However, Benbassat and co-workers showed that FVC, FEV1, and MMFR% were within the predicted values in both type 1 and type 2 diabetes populations (12). Furthermore they compared the effects of type 1 and type 2 diabetes mellitus on the various lung function tests and they showed non-significant differences in FEV1 and MMFR%, but they did not compare their results with the matched control group, this is the most probable reason for this contradiction with the present study (12).

Furthermore type 2 diabetes mellitus, as demonstrated in this study, has significant effects on many lung function tests as compared with the controls, especially during the measurements of FVC%, FEV1 and FEV1/FVC% with statistically significant reductions in the value of these tests. These abnormalities in the lung function tests in this study were the same as what Davis WA and others founds in their study (7).

When we compared the effects of type 1 and type 2 diabetes mellitus on the various lung function tests, there were no much differences between them apart from the FVC% which favors type 1 diabetes mellitus over type 2 diabetes mellitus with highly significant P-value.

This test indicates that type 1 and type 2 diabetes mellitus have more or less similar effects on the various lung function tests. These findings were the same as in other studies (13, 14).

The duration of diabetes in the two groups in the present study seems to have no significant effects on the lung function tests values as most of the patients in the sample studied had their diabetes mellitus duration less than 10 years apart from 5 patients in type 1 and 5 patients in type 2 diabetes mellitus.

Moe SA et al demonstrated in their study that the duration of diabetes in both type 1 and type 2 diabetes mellitus had no significant effects on the lung function tests when the duration of diabetes mellitus is less than 10 years. On the other hand, when the duration of diabetes was more than 10 years or particularly more than 12 years they found statistically significant effects on the various lung function tests (15).

The present study clearly indicates that both type 1 and type 2 diabetes mellitus adversely affect the various pulmonary function tests, and the results are in accord with other previous studies. Analysis of our data demonstrated poor correlation between the number of years of diabetes mellitus and the decline in lung function tests, mostly due to the fact that most of the patients in the present study had their disease for less than 10 years. Even though it is advisable that physicians should think about the lungs as potential targets for end-organ damage in diabetes. For these reasons it is recommended that patients with diabetes should have periodic spirometry measurement to assess their extent of impaired pulmonary function. These measures will recognize early stages of pulmonary defect, which will help to lower the morbidity and mortality of diabetes.

**Conclusion**

Type 1 and type 2 diabetes mellitus adversely affect the various pulmonary function tests. Both types of diabetes cause restrictive ventilator defect. It is probably useful that patients with diabetes should have periodic spirometry measurement to assess the extent of impairment in the pulmonary function tests. These measures will recognize early stages of pulmonary defect, which may help to lower the
morbidity and mortality of patients with diabetes secondary to lung function defect.

Acknowledgment
The authors thank all the staff of respiratory function lab in Ibn-Sena Teaching Hospital, and all the staff of Al-wafa medical center in Mosul for their great help.
The authors also thank Miss Mona Moneer who did all the statistical analysis of the data in this study.

References
Detection of extended spectrum beta-lactamases and antibiogram profile of *Klebsiella* species

Asmaa Z. Al-Gerir
Department of Microbiology, College of Medicine, University of Mosul.

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ABSTRACT

**Objectives:** 1). To determine the prevalence of ESBLs producing *Klebsiella* species. 2). To examine their antibiogram profile. 3). To evaluate the association between ESBLs production and antibiotics resistance in *Klebsiella* isolates.

**Materials and methods:** This prospective study included 116 non repeated isolates of *Klebsiella* species 62 obtained from urine and 54 recovered from wounds. These bacterial isolates were re-identified and tested for antibiotic sensitivity against 19 selected antimicrobial agents. Also, these isolates were evaluated for extended spectrum beta lactamases (ESBLs) by double disk synergy test.

**Results:** Extended spectrum beta lactamases were found to be produced by 16.4% of the total studied *Klebsiella* isolates. Amikacin showed the lowest resistance rate (27.6%), while the highest one was detected against cephalothin, penicillin, cloxacillin and ampicillin (98.3%). The statistical analysis between ESBLs production and antibiotics resistance revealed a significant association only with ceftriaxone (p<0.05), cefotaxime (p<0.001), cefixime (p<0.001), gentamicin (p<0.05) and nitrofurantoin (p<0.05). Moreover, it was found that the strains produced ESBLs showed a higher resistance to all the used antibiotics except for levofloxacin.

**Conclusions:** This study highlights the emergence of ESBLs producing strains of *Klebsiella*, which endowed with extremely wide spectrum of antibiotics resistance including resistance to pencillins, cephalosporin, aminoglycosides and fluoroquinolones. This increased resistance to antimicrobial agents may result in treatment failure.
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The beta lactamases mediated resistance may be overcome by combining beta lactam antibiotics with beta lactamases inhibitor which bind irreversibly to beta lactamases rendering them inactive thus sparing the beta lactam antibiotics (7).

The National Committee for Clinical Laboratory Standards (NCCLS) recommended ESBLs screening method and confirmatory test (8). However, their use in microbiology laboratories has been neglected. Delay in the detection and reporting of ESBLs production by gram negative bacteria is associated with prolonged hospital stay and increased morbidity, mortality and health care costs (9).

Institutional microbial sensitivity tests or local patterns of susceptibility are the first steps that are crucial for treatment of ESBLs producing bacteria.

Aims of the study

The present study was conducted with objectives to determine the prevalence of ESBLs producing Klebsiella species and to examine their antibiogram profile. In addition, to evaluate the association between ESBLs production and antibiotics resistance.

Materials and methods

Bacterial isolates

A total of 116 non-repeated isolates of Klebsiella were collected from 4 different Teaching Hospitals in Mosul- Iraq during a period from September 2010 to January 2011. The specimens yielded these bacterial strains included urine (62) and wound swabs (54). The bacterial isolates were re-identified using the conventional bacteriological and biochemical tests (10).

Antimicrobial sensitivity testing

Antimicrobial sensitivity test was done using disk diffusion method against 19 selected antimicrobial agents according to NCCLS guide lines (11). A bacterial suspension with
turbidity equal to 0.5 McFerland was prepared and this suspension was inoculated on Mueller- Hinton agar plate using a sterile swab. The following antibiotics were tested amikacin (10 mcg), levofloxacin (5 mcg), ciprofloxacin (5 mcg), norfloxacin (10 mcg), enrofloxacin (10 mcg), nalidixic acid (30 mcg), nitrofurantoin (100 mcg), kanamycin (30 mcg), gentamicin (10 mcg), cefotaxime (10 mcg), cefoxitin (30 mcg), pipéracillin (30 mcg), ceftriaxone (10 mcg), cefixime (5 mcg), cefalotin (30 mcg), penicillin (10 mcg), cefuroxime (30 mcg), cefaclor (10 mcg), ampicillin (30 mcg).

Screening for Beta lactamases production
The Klebsiella isolates were tested for their ability to produce beta lactamases using direct rapid iodometric method. These isolates were further tested for their ability to produce ESBLs using double disk synergy test. This test was done to determine the synergy between a disk of amoxicillin/ clavulanic acid (20 mcg/ 10 mcg) and cefotaxime disk (30 mcg). These two disks were placed on inoculated Mueller Hinton agar at a distance of 2.5 mm center to center. A positive result was defined as a 5 mm or more increase in zone of inhibition diameter compared to disk without clavulanic acid (12).

Results
In the present work, 116 isolates of Klebsiella were collected (62 from urine and 54 from wound infection), Klebsiella pneumoniae represented 65.5% of the total isolates, while Klebsiella oxytoca formed 34.5% of the studied microorganisms.

The beta lactamases were detected using the rapid iodometric method, 67.2% of the total Klebsiella strains were rapid beta lactamases producers. Furthermore, the formation of ESBLs in these strains was also evaluated, 16.4% were ESBLs producers while 83.6% of them were non producers (Figure 1).

In the current study, Klebsiella pneumoniae produced ESBLs in a higher percentage than that of Klebsiella oxytoca (11.2, 5.2 respectively). The statistical analysis of ESBLs formation and the difference in species revealed no significant association (Table 1).

Figure (1): Rates of ESBLS producer and non producer in Klebsiella species.

Concerning the site of isolation and ESBLs production, Klebsiella strains isolated from wounds produced ESBLs in a rate of 18.5%, in comparison to 14.5% recovered from urine. However, the statistical analysis showed no significant difference between these two values (Table 2).

The antibiogram profile of Klebsiella isolates was determined against a panel of antimicrobial agents. The microorganism revealed the lowest resistance rate (27.6%) against amikacin, while the highest rate was detected against cephalothin, penicillin, cloxacillin and ampicillin (98.3%) as presented in table 3. Klebsiella isolated from wounds showed a higher resistance rate than those recovered from urine against all the tested drugs except cefoxitin, enrofloxacin, cefotaxime and nalidixic acid (Table 3).

The statistical association between ESBLs production and resistance to antibiotics was evaluated using X² test, the drugs that showed a statistical association were ceftriaxone (p<0.05), cefotaxime (p<0.001), cefixime (p<0.001), gentamicin (p<0.05) and nitrofurantoin (p<0.05). The remaining antibiotics revealed no significant association (Table 4). Although there was no significant statistical difference between resistance to most of the tested drugs and ESBLs formation, the strains produced ESBLs showed a higher resistance to all the used antibiotics except for levofloxacin (Table 4).
Table (1): Percentages of ESBLs production in *Klebsiella pneumoniae* and *Klebsiella oxytoca*.

<table>
<thead>
<tr>
<th>Klebsiella isolates</th>
<th>ESBLs producers No. (%)</th>
<th>ESBL's non-producer No. (%)</th>
<th>Total No. (%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Klebsiella Pneumoniae</em></td>
<td>13 (11.2)</td>
<td>63 (88.8)</td>
<td>67 (65.5)</td>
<td>&lt;0.5</td>
</tr>
<tr>
<td><em>Klebsiella oxytoca</em></td>
<td>6 (5.2)</td>
<td>34 (94.8)</td>
<td>40 (34.5)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>19 (16.4)</td>
<td>97 (83.6)</td>
<td>116</td>
<td></td>
</tr>
</tbody>
</table>

Table (2): Percentages of ESBLs production in wounds and urinary *Klebsiella* isolates.

<table>
<thead>
<tr>
<th>Klebsiella isolates</th>
<th>ESBLs producers No. (%)</th>
<th>ESBL's non-producer No. (%)</th>
<th>Total No. (%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wound</td>
<td>10 (18.5)</td>
<td>44 (81.5)</td>
<td>54</td>
<td>&lt;0.5</td>
</tr>
<tr>
<td>Urine</td>
<td>9 (14.5)</td>
<td>53 (83.5)</td>
<td>62</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>19 (16.4)</td>
<td>97 (83.6)</td>
<td>116</td>
<td></td>
</tr>
</tbody>
</table>

Table (3): Antimicrobial resistance of *Klebsiella* isolates.

<table>
<thead>
<tr>
<th>Antimicrobial agents</th>
<th>% of resistance in urine isolates</th>
<th>% of resistance in wound isolates</th>
<th>% of resistance in total isolates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amikacin</td>
<td>25.8</td>
<td>20.6</td>
<td>27.6</td>
</tr>
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<td>Levofloxacin</td>
<td>22.3</td>
<td>40.7</td>
<td>31</td>
</tr>
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<td>Ciprofloxacin</td>
<td>32.3</td>
<td>37</td>
<td>34.4</td>
</tr>
<tr>
<td>Norfloxacin</td>
<td>35.5</td>
<td>40.7</td>
<td>37.9</td>
</tr>
<tr>
<td>Enrofloxacin</td>
<td>45.2</td>
<td>37</td>
<td>41.3</td>
</tr>
<tr>
<td>Nalidixic acid</td>
<td>41.9</td>
<td>40.7</td>
<td>41.4</td>
</tr>
<tr>
<td>Nitrofurantoin</td>
<td>41.9</td>
<td>48.1</td>
<td>44.8</td>
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<td>51.9</td>
<td>50</td>
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<td>Gentamicin</td>
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<td>69</td>
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<td>81.5</td>
<td>74.1</td>
</tr>
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<td>81</td>
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<td>86.2</td>
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<td>89.9</td>
<td>87.9</td>
</tr>
<tr>
<td>Cephradine</td>
<td>93.5</td>
<td>100</td>
<td>96.8</td>
</tr>
<tr>
<td>Penicillin</td>
<td>96.7</td>
<td>100</td>
<td>98.3</td>
</tr>
<tr>
<td>Cephalothin</td>
<td>96.7</td>
<td>100</td>
<td>98.3</td>
</tr>
<tr>
<td>Cloxacillin</td>
<td>96.7</td>
<td>100</td>
<td>98.3</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>96.7</td>
<td>100</td>
<td>98.3</td>
</tr>
</tbody>
</table>

Table (4): Percentages of antimicrobial resistance and P-value results in ESBLs producer and non producers *Klebsiella* strains.

<table>
<thead>
<tr>
<th>Antimicrobial agent</th>
<th>% of resistance in ESBLs producer isolates</th>
<th>% of resistance in ESBLs non producer isolates</th>
<th>X² test results</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amikacin</td>
<td>42.1</td>
<td>24.7</td>
<td>0.1607</td>
<td>&lt;0.5</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>21.1</td>
<td>32.9</td>
<td>0.5735</td>
<td>&lt;0.5</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>38.6</td>
<td>34</td>
<td>0.0225</td>
<td>&lt;0.5</td>
</tr>
<tr>
<td>Norfloxacin</td>
<td>42.1</td>
<td>37.1</td>
<td>0.022</td>
<td>&lt;0.5</td>
</tr>
<tr>
<td>Enrofloxacin</td>
<td>52.6</td>
<td>39.2</td>
<td>0.696</td>
<td>&lt;0.5</td>
</tr>
<tr>
<td>Nalidixic acid</td>
<td>63.7</td>
<td>37.1</td>
<td>3.434</td>
<td>&lt;0.1</td>
</tr>
<tr>
<td>Nitrofurantoin</td>
<td>68.4</td>
<td>40.2</td>
<td>4.0367</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Kanamycin</td>
<td>57.9</td>
<td>48.5</td>
<td>0.251</td>
<td>&lt;0.5</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>84.2</td>
<td>60.8</td>
<td>4.0169</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Cefotaxime</td>
<td>100</td>
<td>77.7</td>
<td>7.0381</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cefixime</td>
<td>100</td>
<td>69.1</td>
<td>6.3951</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ceftriazone</td>
<td>100</td>
<td>77.3</td>
<td>3.8789</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Cefoxitin</td>
<td>100</td>
<td>91.8</td>
<td>0.643</td>
<td>&lt;0.5</td>
</tr>
<tr>
<td>Piperacillin</td>
<td>100</td>
<td>85.6</td>
<td>1.906</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Cephradine</td>
<td>100</td>
<td>95.9</td>
<td>0.045</td>
<td>&lt;0.5</td>
</tr>
<tr>
<td>Penicillin</td>
<td>100</td>
<td>98.9</td>
<td>0.8411</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Cephalixin</td>
<td>100</td>
<td>98.9</td>
<td>0.8411</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Cloxacillin</td>
<td>100</td>
<td>98.9</td>
<td>0.8411</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>100</td>
<td>98.9</td>
<td>0.8411</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

Discussion

*Klebsiella* is an important nosocomial pathogen that has the potential to cause severe morbidity and mortality. In the present work, *Klebsiella pneumoniae* was isolated from the clinical samples in a higher percentage than *Klebsiella oxytoca*, which was consistent with other workers (13).

The prevalence of ESBLs producing bacteria in most hospitals remains unknown in spite of numerous reports of nosocomial outbreaks of infections due to these microorganisms. In this study, the percentage of *Klebsiella* produced ESBLs was 16.4%, which was in agreement with the result recorded by other researchers (14, 15). On the other hand, Shubla and Ananthan reported a lower incidence (6%) (1), while other worker mentioned a higher (40%) one (16, 17). The occurrence of ESBLs varied from one locality to another, which may be due to infection control practice among different regions or to the difference in the uses of new extended spectrum antimicrobial agents.
**Klebsiella pneumoniae** isolates produced ESBLs in a higher percentage than **Klebsiella oxytoca**. Mulvey and coworkers (2004) reported the same results (13). Furthermore, there was no significant statistical association between the species and ESBLs formation which was in agreement with the findings of Hosoglu and his coworkers (18). This result may be explained on the basis that ESBLs production is plasmid mediated which is transferred to different bacteria regardless of their species. Moreover, the strains isolated from wound infection produced ESBLs in percentage higher than those recovered from urinary isolates, which simulate the work of others (19).

The antibiogram study of **Klebsiella** isolates showed a higher resistance against penicillines and the first and second generation cephalosporines (98.3%); similar results were reported by other researchers (17, 20). The resistance against third generation cephalosporines especially ceftriaxone was high (81%), while cefotaxime and cefixime were more effective agents. Other investigators reported similar results (17), while a lower resistance (64%) was recorded by other investigators (20).

Aminoglycosides have a good effect against the clinically important gram negative bacilli (21). In the current study, amikacin showed the lowest resistance rate (27.96%). This result was similar to the findings (26.96%) of Ullah and his colleagues (20), although it was higher than the result observed by Aminzahed and his coworkers (17) and lower than that of Revathi and Puri (22). Since the least resistance was against amikacin, it may serve as the drug of choice in treating infection caused by **Klebsiella** strains, where the organism showed a resistance rate of 69% and 50% to gentamicin and kanamycin respectively. These results were in concinnity with the work of Ullah and his colleagues (20), while Revathi and Puri (22) reported a less effectiveness of these two drugs.

The observed resistance to ciprofloxacin, norfloxacin, nalidixic acid and nitrofurantoain were 34.4%, 37.9%, 41.4% and 44.8% respectively. These findings were in agreement with the results recorded by another work (17). Ullah and his coworkers (20) recorded a higher resistance rate against ciprofloxacin (52.17%) while Procop and colleagues (23) reported a lower resistance rate (20%). Moreover, the resistance percentage against levofloxacin was 31%, so this drug might be still a good choice for treatment of infections caused by **Klebsiella**.

A significant statistical difference in susceptibility profile between ESBLs producers and ESBLs non producers **Klebsiella** species to ceftriaxone, cefotaxime and cefixime, was recorded during the study. These findings were consistent with the results of other workers (24). Also, there was a significant difference between gentamicin and nitrofurantoin which goes with the work of Procop and colleagues (23). The resistance to ciprofloxacin, amikacin and nalidixic acid had no significant differences with the production of ESBLs which were inconsistence with another study (23).

Furthermore, the **Klebsiella** strains produced ESBLs were more resistant to almost all the tested antimicrobial agents than the non producer ones, similar observation has been reported by Mulvey and his coworkers (13). This high antibacterial resistance in ESBLs producing microorganisms has caused major therapeutic problems all over the world. These findings support the hypothesis that ESBLs producing strains were more likely to have diminished susceptibility to non-beta lactam antibiotics as well as beta lactam ones compared with ESBLs non-producing isolates. Therefore, the accurate detection and reporting of ESBLs production in clinical isolates is of great importance.

**Conclusion**

This study highlights the emergence of ESBLs producing strains of **Klebsiella**, which endowed with extremely wide spectrum of antibiotics resistance including resistance to penicillins, cephalosporins, aminoglycosides and fluoroquinolones. This increased resistance to antimicrobial agents may cause failure in treatment of infection caused by these microorganisms. Due to the importance of ESBLs producing organisms and difficulty in
treatment of infection caused by these bacteria, there is a necessity for rapid identification of ESBLs. Therefore, clinical laboratories should adopt simple test based on CLSI recommendations for confirming ESBLs production in enterobacterial species and doing antimicrobial susceptibility test for precise treatment thus, avoiding haphazard therapy.

References
12. National Committee for clinical Laboratory Standards 2005. Performance standards for antimicrobial susceptibility testing .15th informational supplement (M100-s15) NCCLS.


Effects of carbamazepine on serum leptin, insulin levels and oxidative stress in epileptic patients

Imad A. Thanoon*, Othman A. Pachachi**, Mohammed M. Al-Sheikh***

* Department of Pharmacology, *** Department of Medicine, College of Medicine, University of Mosul; ** Department of Clinical Pharmacy, College of Pharmacy, University of Mosul.


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ABSTRACT

Objectives: To assess the effect of carbamazepine (CBZ) monotherapy in male adult epileptic patients on serum leptin, insulin levels, body mass index and oxidative stress represented by serum malondialdehyde (MDA) in comparison to healthy controls.

Patients and methods: To achieve the aims of the current study, a case-control study design was adopted. A total of 38 male adult patients with primary generalized epilepsy, on continuous CBZ monotherapy, for at least six months before participation in the study, were collected over the period from Sept. 2010 to Jan. 2011. Forty apparently healthy male volunteers without previous history of epilepsy were recruited as controls. Fasting blood samples were taken and sera were separated and used to measure serum levels of leptin and insulin, and MDA. Body mass index (BMI) was calculated as weight in kilograms divided by the squared height in meters.

Results: The results of this study revealed that there was insignificant difference in BMI, serum leptin and insulin between male epileptic adult patients and their matched control subjects. The results also revealed that male epileptic adult patients had a significantly higher (p<0.001) serum MDA compared to their matched control subjects.

Conclusion: Carbamazepine is a relatively low risky antiepileptic drug (AED) in terms of obesity, while it can cause oxidative stress as reflected by an elevated serum MDA in comparison to controls.

Keywords: Epileptic patients, carbamazepine, BMI, leptin, insulin, malondialdehyde
M any types of endocrine and metabolic dysfunctions are associated with epilepsy and its medications that may impair individual’s overall function.\(^\text{1,2}\) Epilepsy and its medications are associated with weight changes in which weight gain is the most common and distressing problem.\(^\text{3}\) Weight gain is a difficult problem at any age, particularly in adolescence, a period of increased awareness to body weight and image.\(^\text{4}\) Weight gain not only affects body image and self-confidence with adverse psychological effects leading to non-compliance to medications,\(^\text{5}\) but also associated with pathologic consequences related to obesity as dyslipidemia, hypertension, diabetes mellitus and atherosclerosis with its related vascular complications.\(^\text{6}\) Epilepsy and antiepileptic drugs(AEDs) may alter weight homeostasis regulating process including the two main homeostatic hormones, leptin and insulin. Increased blood levels of leptin and insulin due to leptin and insulin resistances are observed in patients with epilepsy.\(^\text{7,8}\)

Leptin controls weight homeostasis through two main neuropeptidergic systems that both project into the arcuate nucleus, neuropeptide Y(NPY) and pro-opiomelanocortin (POMC) expressing neurons.\(^\text{9,10}\) These neurons exert two opposite functions. NPY expressing neurons are anabolic, upon stimulation, food intake and metabolic efficiency are increased while energy expenditure is decreased. In contrast, the counterpart POMC expressing neurons are catabolic, upon stimulation, food intake and metabolic efficiency are decreased while energy expenditure is increased.\(^\text{11}\)

It has been reported that increased generation of free radicals or decreased activity of antioxidant defense systems can cause some forms of seizures and in addition can increase the risk of seizure recurrence.\(^\text{12,13}\) Many AEDs are metabolized to generate reactive metabolites with the capability of covalent binding to macromolecules as proteins or other vital biomolecules and hence eliciting systemic toxicity.\(^\text{13,14}\) Lipid peroxidation caused by increased generation of free radicals or decreased activity of antioxidant defense systems have been suggested to be critically involved in seizure control.\(^\text{12}\) The aims of this study are to assess the effect of CBZ monotherapy in male epileptic patients on BMI, serum leptin, insulin and MDA levels (as a representative of oxidative stress), in comparison with healthy controls.

**Patients and methods**

**A. Epileptic patients**

This study included 38 male adult patients with primary generalized epilepsy, on continuous carbamazepine (CBZ) (Tegretol) [Novartis, Switzerland] monotherapy, for at least six months before participation in the study. These patients were referred from the private clinic of a consultant neurologist over the period from Sept. 2010 to Jan. 2011. Patients with the following criteria were excluded from this study:

1. Patients with secondary epilepsy.
2. Patients with other neurological, medical, or psychiatric disorders.
3. Patients with rapidly progressive disorders that could alter their weight.
4. Patients with family history of body weight disorders.
5. Patients treated with other AEDs beside CBZ.
6. Patients treated with CBZ for less than six months.

Approval to conduct this study was obtained from the ethical committee of the Local Health Authority in Mosul City and from the College of Medicine-University of Mosul. Blood samples were taken from them and assay of serum leptin, MDA and insulin levels were done.

B. Control subjects
Forty apparently healthy male volunteers without previous history of epilepsy were recruited as controls with age matching to the patients group. The control group was judged free of any illness by history and clinical examination. They were included in the study to compare the normal values for serum leptin, insulin and MDA levels.

C. Specimen collection and analysis
Samples from the control (friends and relatives) and the patients were collected and assay of serum levels of leptin, insulin, MDA and TAS were done as in the patients group. Serum leptin was measured by enzyme linked immunosorbent assay (ELISA) technique, using the IBL leptin ELISA Kit (Germany), which is an immunoassay for the quantitative in vitro diagnostic measurement of leptin in serum and plasma. Serum insulin was also measured by ELISA kit (DRG-Germany). Serum MDA levels were measured using TBA assay method. Body mass index (BMI) was calculated using the following equation:

\[
\text{BMI} = \frac{\text{Weight (Kg)}}{\text{Height (m}^2)\text{)}^{16}
\]

Statistical analysis
The data obtained in the current study were analyzed using Statistical Package for Social Sciences (SPSS) (version 16). Standard statistical methods were used to determine the mean and standard deviation. Unpaired t-test was used to compare the results of different biochemical parameters of epileptic adult patients with their matched controls.

Results
Table (1) and (2) demonstrated the demographic characteristics of the male epileptic adult patients and their matched control subjects respectively.

Table (3) demonstrated the comparison of BMI, serum levels of leptin, insulin and MDA between male epileptic adult patients receiving continuous CBZ monotherapy and their matched control subjects.

The results of this study revealed that there was insignificant difference in BMI, serum leptin and insulin between male epileptic adult patients receiving continuous CBZ monotherapy and their matched control subjects. The results also revealed that male epileptic adult patients on continuous CBZ monotherapy had a significantly higher \( p<0.001 \) serum MDA compared to their matched control subjects.

Table (1): The characteristics of the male epileptic adult patients.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Mean± SD Number=38</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients age (years)</td>
<td>29.54±5.36</td>
</tr>
<tr>
<td>Body mass index (BMI) (kg/m²)</td>
<td>24.59±2.92</td>
</tr>
<tr>
<td>Duration of illness (years)</td>
<td>3.25±2.05</td>
</tr>
<tr>
<td>Duration of using CBZ (months)</td>
<td>25.09±20.08</td>
</tr>
<tr>
<td>Dose of CBZ (mg/day)</td>
<td>590.90±144.44</td>
</tr>
</tbody>
</table>

Table (2): The characteristics of the control adult subjects.

<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>Subjects age (years)</td>
<td>30.05±5.95</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>23.33±1.91</td>
</tr>
</tbody>
</table>

Table (3): BMI and serum levels of leptin and malondialdehyde (MDA) in the male epileptic patients and their matched control subjects.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Epileptic patients</th>
<th>Control subjects</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI (kg/m²) Mean ± SD</td>
<td>24.59±2.92</td>
<td>23.33±1.91</td>
<td>NS</td>
</tr>
<tr>
<td>Leptin (ng/ml) Mean ± SD</td>
<td>4.60±1.20</td>
<td>3.91±1.96</td>
<td>NS</td>
</tr>
<tr>
<td>MDA (µMol/L) Mean ± SD</td>
<td>1.88±0.19</td>
<td>0.95±0.22</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Insulin (mU/L) Mean ± SD</td>
<td>8.37±7.2</td>
<td>8.56±7.00</td>
<td>NS</td>
</tr>
</tbody>
</table>

NS: statistically non-significant
Discussion

Epilepsy is a common chronic neurological problem. Its treatment is often for years or even lifelong.\(^{17}\) It should be noted that patients with epilepsy may manifest metabolic adverse effects throughout the course of their management with anti-epileptic drugs (AEDs), which on long-term may impair individual’s overall function.\(^{18}\) Clinically significant weight gain has been reported with several AEDs including the conventional agents valproate (VPA), CBZ and the newer medications gabapentin and vigabatrin and may result in lack of compliance with or even discontinuation of therapy.\(^{19}\) Numerous studies reported weight gain with VPA in up to 50—70% of the patients.\(^{3,20,21}\) Its etiology is most likely multi-factorial and controversial. Weight gain appears to be less a problem with CBZ than with VPA. The proposed mechanism of CBZ-associated weight gain can arise from edema but has also been associated with increased appetite and food consumption in the absence of edema.\(^{22}\) The CBZ-induced edema has been postulated to be caused by drug-induced alterations in the secretion of antidiuretic hormone (ADH), although studies only inconsistently show an effect of the drug on plasma ADH levels.\(^{23}\)

Our study revealed insignificant effect of CBZ on BMI which is consistent with the studies of Biton,\(^{24}\) and Uludag et al\(^{25}\) but inconsistent with the studies of Richens et al\(^{26}\) and Hogan et al.\(^{27}\) They reported that between 15% and 25% of patients treated with CBZ developed weight gain. The two common homeostatic hormones, insulin and leptin have been expected to form a common link to weight gain in epilepsy with the use of some AEDs. Our study also revealed insignificant effect of CBZ on serum leptin level and insulin. Rauchenzauner et al.\(^{28}\) compared two patient groups that use VPA and non-VPA AEDs regarding serum leptin and insulin levels. They concluded that non-VPA AEDs, (lamotrigine and oxcarbazepin) were thought to have no effect on leptin and insulin levels. There are a few studies such as ours that evaluate effect of CBZ treatment directly on serum leptin and insulin levels. Our findings are consistent with the results of Uludag et al and Hamed et al.\(^{25,29}\)

Our study reported an elevated serum MDA level in epileptic male patients on CBZ therapy in comparison with healthy controls. Our findings are consistent with the results of the study conducted by Aycicek and Iscan.\(^{30}\) They reported a markedly increased serum total peroxide levels in CBZ treated and untreated epileptic patients compared to healthy controls. Solowiej and Sobaniecz\(^{31}\) on studying the effect of CBZ and VPA therapy on antioxidant enzyme activity and serum lipid peroxidation in young epileptic patients, concluded that MDA concentration was elevated in all epileptic patients, significantly both in VPA monotherapy and in polytherapy, while insignificantly in newly diagnosed epileptics and in CBZ monotherapy. In agreement with our findings the study conducted by Nemade et al.\(^{32}\) They reported that epileptic patients on regular or irregular treatment (phenytoin and CBZ), have an increased serum leptin and insulin levels. There are a few studies such as ours that evaluate effect of CBZ treatment directly on serum leptin and insulin levels. Our findings are consistent with the results of Uludag et al and Hamed et al.\(^{25,29}\)

Our study reported an elevated serum MDA level in epileptic male patients on CBZ therapy in comparison with healthy controls. Our findings are consistent with the results of the study conducted by Aycicek and Iscan.\(^{30}\) They reported a markedly increased serum total peroxide levels in CBZ treated and untreated epileptic patients compared to healthy controls. Solowiej and Sobaniecz\(^{31}\) on studying the effect of CBZ and VPA therapy on antioxidant enzyme activity and serum lipid peroxidation in young epileptic patients, concluded that MDA concentration was elevated in all epileptic patients, significantly both in VPA monotherapy and in polytherapy, while insignificantly in newly diagnosed epileptics and in CBZ monotherapy. In agreement with our findings the study conducted by Nemade et al.\(^{32}\) They reported that epileptic patients on regular or irregular treatment (phenytoin and CBZ), have an increased serum leptin and insulin levels. There are a few studies such as ours that evaluate effect of CBZ treatment directly on serum leptin and insulin levels. Our findings are consistent with the results of Uludag et al and Hamed et al.\(^{25,29}\)

In conclusion CBZ monotherapy can be regarded as a safe drug with regard to BMI, serum leptin and insulin levels, but it can cause oxidative stress as represented by elevated serum MDA levels.

References


Value of clinical data in diagnosis of symptomatic celiac disease in children

Nashwan M. Al-Hafidh
Department of Medicine, Pediatric Division, Nineveh College of Medicine, University of Mosul.

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ABSTRACT

Objective: To identify the value of clinical data in diagnosis of celiac disease (CD) in children.

Patients and methods: a prospective study was conducted in Mosul city during the period from 30th of October 2007 to 30th of April 2011. A total of 57 patients (39 males, 18 females) aged more than 6 months on gluten containing diet presented with symptoms suggestive of (CD) were evaluated clinically and serologically using IgA human recombinant tissue transglutaminase antibody. (IgA anti tTG2). Multiple duodenal biopsies were performed for every patient enrolled in this study. CD cases had been followed up 6 months after a gluten free diet (GFD) by weight measurement and the mentioned serological testing.

Results: A total of 29 (50.9%) out of 57 symptomatic patients with mean age of 56.1 months, demonstrated positive biopsy results for celiac disease. Failure to thrive (FTT) was noticeable in 25 (86.2%) of studied patients with celiac disease followed by anemia, abdominal distension, offensive stool and chronic diarrhea in decreasing frequency. Catch up of weight was not achieved in 10 (43.5%) out of 23 CD patients with FTT whose (IgA anti tTG2) normalized after 6 months of GFD.

Conclusions: The diagnosis of celiac disease on the basis of clinical features alone was incorrect in (49.1%) cases, indicating that diagnosis and lifelong GFD treatment is not justifiable relying on clinical data. Catch up of weight cannot be relied upon as an early marker of clinical improvement in patients with proven adherence to GFD. The result of this study emphasizes the importance of increasing awareness of the accurate tools in diagnosis of CD in children based on serological and biopsy evidences.

Keywords: Celiac disease, clinical diagnosis, catch up of weight.
Celiac disease (CD) is an immune-mediated enteropathy caused by permanent sensitivity to gluten in genetically susceptible individuals (1). It occurs in genetically predisposed individuals (2) and marked geographical variations do appear to exist (3).

The prevalence of celiac disease in Tunisian schoolchildren, estimated to be about 1/157 which is close to the European prevalence (2). In Jordan the serological prevalence was estimated to be 1:124 in schoolchildren (4), whereas the average annual incidence in Kuwait is 1:3000(5). To date no prevalence of celiac disease data were reported from Iraq.

Symptoms can begin at any age when gluten-containing foods are given; typical symptoms include diarrhea, offensive stools, abdominal distention, decreased appetite, failure to thrive, and iron-deficiency anemia not responding to oral iron therapy, edema and short stature (1,6,7). It is recommended that CD be an early consideration in the differential diagnosis of children with FTT and persistent diarrhea. Limited data suggest the prevalence of CD may be increased 2–10 times in children with some of these GI symptoms or occur in up to 5% of cases (8).

Definitive diagnosis of celiac disease requires small intestinal biopsy (1). According to the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN), there is a recognized spectrum of histologic features varying from mild to severe as described by Marsh et al (8). Marsh classified the histologic changes of CD as Type 0 or preinfiltrative stage (normal), Type 1 or infiltrative lesion (increased intraepithelial lymphocytes), Type 2 or hyperplastic lesion (Type 1+ hyperplastic crypts), Type3 or destructive lesion (Type 2 + variable degree of villous atrophy) and Type 4 or hypoplastic lesion (total villous atrophy with crypt hypoplasia) (8). None of the individual features is pathognomonic for CD, as each may be seen in other disease states however, the combination of histopathologic features in a compatible clinical setting is sufficient evidence for a diagnosis of CD and there is good evidence that villous atrophy (Marsh Type 3) is clearly a feature of CD (8,9). Despite the increasing importance of serological methods, the diagnosis of CD is still based on histological criteria (8-10) followed by a therapeutic response to a gluten free diet (9).

The mucosal involvement can be patchy, so multiple biopsies must be obtained (1).

Given the lifelong nature of the disease, the attendant need for an expensive socially inconvenient gluten free diet (GFD) and the sporadic local practice of a trial of GFD without confirmations of CD diagnosis in spite of availability of CD serological screening tests leads the investigator to assess the value of clinical data in diagnosis and follow up of CD in relation to investigational tools.

Patients and methods
A prospective study conducted at private clinic in Mosul city during the period from 30th of October 2007 to 30th of April 2011. Patients selected in the study were aged more than 6 months and on gluten containing diet, with various combinations of symptoms and signs suggestive of CD including chronic diarrhea, abdominal distention, offensive stool, anorexia, positive family history of CD in first degree relative, anemia defined according to...
age and sex related hemoglobin levels and failure to thrive (FTT) defined as weight <5\textsuperscript{th} centile for age and sex.

A total of 57 patients (39 males, 18 females) with mean age of 56.1 months, were evaluated by history and physical examination. They were screened by serological testing using second generation ELISAs IgA human recombinant tissue transglutaminase antibody (IgA anti tTG2) which was done by commercially available kit (AESKULISA tTG-A 3503/ Germany). Esophagastroduodinoscopy and biopsy was done in Alsalam General Hospital in Mosul city where three sites of duodenum were biopsied from every patient. Biopsy specimens were evaluated in the same hospital and pathology reports were analyzed according to Marsh criteria \(^{(4)}\).

Patients were reevaluated 6 months after GFD by weight measurements and same serological test.

Verbal consents were approved regarding clinical, hematological testing along with written informed consents were taken from parents of all children before endoscopic duodenal biopsy. The ethical committee approved this study.

Data analysis was done using SPSS program. Chi squared test was used for measurement of statistical significance.

**Results**

A total of 29 (50.9\%) out of 57 symptomatic patients [18 males (62.1\%) and 11 females (37.9\%)] demonstrated positive biopsy results consistent with CD diagnosis; whereas the remaining 28 (49.1\%) cases had normal biopsy results. Although 66.7\% of patients with positive family history and 85.7\% of patients with dimorphic anemia had positive biopsy of CD, all the studied clinical variables were not significantly associated with biopsy results (Table 1).

Table (1): Sensitivity, specificity, predictive values, accuracy and significance of clinical variables suggestive of CD in comparison to results of duodenal biopsy.

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>Biopsy of studied cases</th>
<th>Sensitivity %</th>
<th>Specificity %</th>
<th>+ve predictive value</th>
<th>-ve predictive value</th>
<th>Accuracy</th>
<th>P-VALUE*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total No.</td>
<td>%</td>
<td>No.</td>
<td>%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptoms</td>
<td>Total</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic diarrhea</td>
<td>38</td>
<td>17</td>
<td>44.7</td>
<td>21</td>
<td>55.3</td>
<td>59</td>
<td>25</td>
</tr>
<tr>
<td>Offensive stool</td>
<td>42</td>
<td>23</td>
<td>54.8</td>
<td>19</td>
<td>45.2</td>
<td>79.3</td>
<td>32.1</td>
</tr>
<tr>
<td>Abdominal distension</td>
<td>46</td>
<td>24</td>
<td>52.2</td>
<td>22</td>
<td>47.8</td>
<td>82.8</td>
<td>21.4</td>
</tr>
<tr>
<td>Anorexia</td>
<td>41</td>
<td>19</td>
<td>46.3</td>
<td>22</td>
<td>53.7</td>
<td>65.5</td>
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<tr>
<td>Family history</td>
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<tr>
<td>Failure to thrive</td>
<td>48</td>
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<td>23</td>
<td>47.9</td>
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<tr>
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<td>26</td>
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<td>1</td>
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<td>0</td>
<td>1</td>
<td>100</td>
<td>0</td>
<td>96.4</td>
</tr>
</tbody>
</table>

*P- value: value less than 0.05 is considered significant.
Clinical features of studied patients with positive biopsy of CD showed that FTT was noticeable in 25 (86.2%) of patients followed by anemia, abdominal distension, and offensive stool in decreasing frequency. In 17 patients (58.6 %) who had CD had chronic diarrhea (Table 2).

IgA anti- tTG2 test was above the cut-off value of the used kit for a positive result which is more than 15 U/ml in 29 (50.9%) patients; all of them demonstrated a positive biopsy result suggestive of CD. On the other hand those with normal biopsy results had negative serological values.

Marsh type 3 histological grading was evident in 27 (93.1%) patients whereas Marsh type 1 grade was displayed in 1 (3.45%) case and Marsh type 2 grades in the other (Table 3).

Follow up of CD cases 6 months after GFD showed that catch up of weight was not achieved in 10 (43.5%) out of 23 CD patients with FTT whose (IgA anti tTG2) otherwise became normal. The remaining 2 CD patients with FTT had failure of catching up of weight, failure of serological normalization in conjunction with unchanging Marsh type 3 histological grading on repeated biopsy.

Table (2): Clinical features of 29 patients with positive biopsy of celiac disease.

<table>
<thead>
<tr>
<th>Patients with positive biopsy of CD Cases (n=29)</th>
<th>Variables</th>
<th>No.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms</td>
<td>Chronic diarrhea</td>
<td>17</td>
<td>58.6</td>
</tr>
<tr>
<td></td>
<td>Normal bowel motion</td>
<td>12</td>
<td>41.4</td>
</tr>
<tr>
<td></td>
<td>Offensive stool</td>
<td>22</td>
<td>75.9</td>
</tr>
<tr>
<td></td>
<td>Abdominal distension</td>
<td>23</td>
<td>79.3</td>
</tr>
<tr>
<td></td>
<td>Anorexia</td>
<td>19</td>
<td>65.5</td>
</tr>
<tr>
<td></td>
<td>Positive family history</td>
<td>4</td>
<td>13.8</td>
</tr>
<tr>
<td>Signs</td>
<td>Failure to thrive</td>
<td>25</td>
<td>86.2</td>
</tr>
<tr>
<td></td>
<td>Edema</td>
<td>1</td>
<td>3.4</td>
</tr>
<tr>
<td></td>
<td>Anemia</td>
<td>24</td>
<td>82.8</td>
</tr>
<tr>
<td></td>
<td>Hypochromic microcytic</td>
<td>18</td>
<td>62.1</td>
</tr>
<tr>
<td></td>
<td>Dimorphic</td>
<td>6</td>
<td>20.7</td>
</tr>
</tbody>
</table>

Marsh type 1 grade was displayed in 1 (3.45%) case and Marsh type 2 grades in the other (Table 3).

Table (3): Clinical features of 29 celiac disease cases in relation to histopathological grading.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total</th>
<th>No.</th>
<th>%</th>
<th>No.</th>
<th>%</th>
<th>No.</th>
<th>%</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic diarrhea</td>
<td>17</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>5.9</td>
<td>16</td>
<td>94.1</td>
<td>0.257</td>
</tr>
<tr>
<td>Offensive stool</td>
<td>23</td>
<td>1</td>
<td>4.3</td>
<td>1</td>
<td>4.3</td>
<td>21</td>
<td>91.3</td>
<td>0.697</td>
</tr>
<tr>
<td>Abdominal distension</td>
<td>24</td>
<td>1</td>
<td>4.2</td>
<td>1</td>
<td>4.2</td>
<td>22</td>
<td>91.6</td>
<td>0.903</td>
</tr>
<tr>
<td>Anorexia</td>
<td>19</td>
<td>1</td>
<td>5.3</td>
<td>1</td>
<td>5.3</td>
<td>17</td>
<td>89.4</td>
<td>0.481</td>
</tr>
<tr>
<td>Positive family history</td>
<td>6</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>4</td>
<td>66.7</td>
<td>0.776</td>
</tr>
<tr>
<td>Signs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Failure to thrive</td>
<td>25</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>4</td>
<td>24</td>
<td>96</td>
<td>0.109</td>
</tr>
<tr>
<td>Edema</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>100</td>
<td>0.957</td>
</tr>
<tr>
<td>Hypochromic microcytic anemia</td>
<td>18</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>5.6</td>
<td>17</td>
<td>94.4</td>
<td>0.140</td>
</tr>
<tr>
<td>Dimorphic anemia</td>
<td>6</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>6</td>
<td>100</td>
<td>0.411</td>
</tr>
</tbody>
</table>

*P- value: value less than 0.05 is considered significant.
Discussion

In 29 (50.9%) of studied cases, the diagnosis was correct based on clinical data, the positive predictive values of the majority of selected variables ranged approximately between (44%-54%) as an indicative of celiac disease diagnosis based on clinical manifestation. These findings support the recommendations of (NASPGHAN) (8), signifying the value of history and examination in selecting symptomatic patients for screening for CD. It has been estimated that the prevalence of celiac disease in children between 2.5 and 15 yr in the general population ranges from 3 to 13/1,000 children or ≈1/300 to 1/80 children (1), screening of patients with symptoms of celiac disease resulted in increase detection of CD from 3-13/1,000 children in the general population to 50.9% according to this study.

The diagnosis of celiac disease on the basis of clinical features alone was incorrect in 28(49.1 %) studied cases, similar results have been observed in other studies which showed that a clinical diagnosis in children on the basis of gastrointestinal symptoms alone was incorrect in more than 50% of cases (11-12), signifying that diagnosis and lifelong GFD treatment is not justifiable relying on clinical diagnosis alone.

The male: female ratio of the children with CD was 3:2 in the study done by Ujjal et al (13), which is similar to the present study results.

Although the sensitivity of some variables (offensive stool, abdominal distention, FTT and anemia) was high (close or over 80%) their specificity was low (around 20%), furthermore the studied clinical variables were not significantly associated with biopsy results (p-value >0.05), these may be explained by the fact that these clinical variables are common shared manifestations of other diseases that CD should be differentiated from (3).

In (58.6%) of studied CD patients had chronic diarrhea, comparable results were present in other studies (14-15). In 41.4% of celiac cases in this study had normal bowel motion, Telega et al found that 28.2% of his cases had diarrhea and 5.1% had constipation suggesting that the remaining 66.7% had normal bowel motion (16), indicating that normal bowel motion does not preclude the possibility of CD diagnosis. Offensive stool was the compliant of (75.9 %) of our celiac disease patients compared to 50% in other study (1) which might be related to the severity and extent of mucosal damage. Abdomen was distended in (79.3 %) of studied CD patients, similar results (80%) were found by Khuffash et al (5). Anorexia presented in two thirds of our cases which are concordant with the finding in other studies (1, 17).

Kuloğlu et al in Turkey observed failure to thrive in 34.8% of cases of CD (18) and Telega et al in Southeastern Wisconsin found that 25.4% of cases with CD presented with FTT (16). While FTT was reported in 100% of cases with CD in Arabic studies conducted by Al-Hassany et al in Iraq (19), Khuffash et al (5) in Kuwait and Al-Tawaty et al in Libya (20). FTT reported in 91% of CD patients in India (21). In our study (86.2%) of CD cases present with FTT. This high frequency of FTT may be attributed to delayed diagnosis, severity of mucosal damage with malabsorptive consequences or concomitant malnutrition. Less common presentations of celiac disease include hypoproteinemia secondary to protein-losing enteropathy manifested by edema which was evident in 3.4 % of studied patients.

Rashid et al found that 8% of the children had a first-degree relative with biopsy-confirmed celiac disease (23), while family history was positive in 21% in the study conducted by D’Amico et al in USA (24). In our study positive family history was found in (13.8%) of cases, similar result was found by Barker et al (7). This difference may be attributed to the heterogeneity of the studied populations, subject selection, different genetic susceptibility and rate of consanguineous marriages. Positive family history was the positive predictor of CD diagnosis in 66.7% of cases before the diagnosis was histologically confirmed, having specificity of 92.8%. The result found in our study supports the routine testing of asymptomatic children who are first-degree relatives of confirmed celiac disease recommended by (NASPGHAN).

Anemia is still a common presentation of celiac disease (25). Hypochromic microcytic
morphology was the most frequent type associated with CD cases in this study, which is concordant with the finding in other studies (14,16,17). In 43.9% of cases in this study hypochromic microcytic anemia was among the presenting findings leading to the diagnosis of celiac disease, similar result was found in Greek by Karyda et al (26) and in Basrah by Mansoor et al (27). Whereas higher results were found by Hashim et al (28), this may be related to the sample selection and time of diagnosis. Overall all these results support the recommendations of (NASPGHAN) that persistent iron deficiency anemia is an indication for celiac screening (4). Dimorphic anemia was present in 20.7% of studied cases with celiac disease and Patwari et al also found that 20% of CD had dimorphic anemia (29) nevertheless it was the foreteller of the diagnosis in 85.7% of studied cases as a positive predictor of CD before biopsy results appeared and having a specificity of 96.4%. These high values may be related to the severity of mucosal injury in view of the fact that all studied patients with dimorphic anemia had Marsh 3 histopathological grading.

Overall, the severity of symptoms associated with celiac disease is highly variable, and in large part this reflects the severity and extent of mucosal damage (3), which explain the more frequent symptoms in our patients with Marsh 3 histopathological changes. The reported prevalence of GI manifestations has varied widely among different studies; this may be due to the low number of patients evaluated or a delay in their presentation (30).

Catch-up growth is characterized by an increased growth velocity in height and/or weight after the removal of some constraint on normal growth, this increased velocity brings a child’s height-for-age or weight-for-age status back toward the normal centiles (31). Treatment with GFD did not result in an overall significant increase in weight-for-height score up to 4 years of follow-up (32). Mean weight-for-height returned to normal 15 months after dietary treatment (33). Failure of the anti-tTG level to decline over a period of 6 months after starting the GFD suggests continued ingestion of gluten or related products (4). Catch up of weight was not achieved in 10 (43.5%) out of 23 enrolled CD patients with FTT whose (IgA anti-tTG2) normalized after 6 months of GFD, indicating that catch up of weight may be delayed, cannot be relied upon as an early marker of clinical improvement in patients with proven adherence to GFD manifested by normal serological monitoring as well as in patients on trial of GFD without disease confirmation.

The result of this study albeit reflecting private clinic statistics, evidently illustrated that celiac disease manifestations is a useful tool to initiate an effective serological screening tests rather than a tool to label a diagnosis and permanently treat assumed celiac disease without based evidence, along with erroneous follow up of manifestation rather than the disease. As in no case should false information given to the patient, this study notify a doctor about percentages of incorrect decisions made depending only on clinical experience of CD, which ultimately affect patient health in addition to its impact on social, financial and psychological aspects of patient life and also reflects the ethical and medical responsibility of the doctor toward his patient aiming to give optimum quality of available medical care. The result of this study emphasizes the importance of the patient human rights to get an evidently based accurate diagnosis of celiac disease before permanent changing of dietary life style.

References
4. Nusier MK, Brodtkorb HK, Rein SE, Odeh A, Radaideh AM, Klungland H. Serological screening for celiac disease in...


Assessment of physical environment of primary schools in Mosul city

Waleed G. A. Al-Taee**, Redhaa Abd-Alhameed Al-Tuhafee*

* M.sc. Candidate, **Department of Community Medicine, College of Medicine, University of Mosul.

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ABSTRACT

Background: Physical school environment considered one of the critical points for children growth and development. Schools are large places that present significant opportunities for getting an accident or infection.

Objective: To assess the physical environmental health criteria of primary schools in Mosul city.

Methods: A descriptive cross sectional study design has been adopted. A sample of 25 schools has been taken using multi-stage stratified stratum sampling technique. A special questionnaire form has been prepared depending on WHO criteria for schools environment. A separate questionnaire form has been filled by the investigator herself for each school.

Results: Study results revealed that 52% of the schools are near a main street, 80% of schools are close to sources of pollution specially garbages, 20% of schools have maintained gardens, 72% of schools have inadequate faucets, 92% of schools have inadequate toilets. Whereas only 24% of toilets founds have good sanitary conditions. On the other hand only 20% of classrooms were found to be appropriate, 48% of schools were having inadequate lighting and 28% have inadequate ventilation.

Keywords: School environment, primary school, physical.
important to provide an environment that is wholesome and supportive of learning\(^2\). As society continues to focus on the importance of academic achievement, the school physical environment should be addressed as a critical factor that influences academic outcomes\(^3\).

The physical school environment encompasses the school building and all its contents, the site on which a school is located and the surrounding environment including the air, water, and materials with which children may come into contact, as well as nearby land uses, roadways and other hazards\(^4\).

The American Academy of Pediatrics defines a "healthful school environment" as "one that protects students and staff against immediate injury or disease and promotes preventive activities and attitudes against known risk factors that might lead to future disease or disability"\(^5\).

It is important to the health of school children to have clean water to drink, enough water to use for hygiene, adequate sanitation facilities, clean air to breathe, safe and nutritious food, and a safe place to learn and play. A contaminated environment can cause or exacerbate health problems. These include short-term health effects such as infectious diseases, respiratory infections and asthma that can reduce school attendance and learning ability. Health effects such as cancer or neurological diseases may be delayed until much later in life, on the other hand a healthy school environment can directly improve children's health and effective learning and thereby contribute to the development of healthy adults as skilled and productive members of society. Furthermore, schools act as an example for the community; students who learn about the link between the environment and health will be able to recognize and reduce health threats in their own homes\(^6\).

Study aim is to assess the physical environmental health criteria of primary schools in Mosul city.

**Subjects and methods**

Preliminary official permissions were obtained from both General Directorates of Health and Education in Nineveh Governorate.

A descriptive cross sectional study design was adopted. Study period was two months, from the first of December 2010 to the end of January 2011. Study material was 25 primary schools all taken through a multi-stage stratified stratum sampling technique from a total of 280 primary school buildings in Mosul city. To start with primary schools of Mosul City have been divided into two groups (one at right side of Tigris River and the other at left side of the river). Later, the school of each group has been divided into schools for girls and for boys. Finally sample of schools has been selected according to simple random technique. Accordingly, a total 14 schools at left bank (7 schools for boys and 7 for girls) and 11 schools at right bank (5 schools for boys, 5 for girls and one mixed school) have been chosen as a study material. A special questionnaire form has been prepared utilizing the WHO criteria for physical school environment\(^6\) and taking in consideration the consultation advise of specialized physicians at school health services sector in Mosul. The questionnaire form items included the following:

1. **Area surrounding the school** which includes distance between school and main street (ideally it must be more than 150 meters\(^6\)) and presence and type of pollution sources nearby the school.

2. **School environment** which includes school wall height (standard height is 1.8-2 meters), school yard availability and adequacy (adequate school yard means 1-1.5 square meter/ student, including buildings, gardens and playgrounds) school cleanliness, power sources, garbage containers availability and state (standard garbage containers must have a lid), daily disposal of waste, chlorine levels checking, state and adequacy of faucets (standard water faucets means one faucet/50 students with the nozzle facing upwards and higher than edge of basin) and toilets adequacy and sanitation (one toilet per 25 students, constructed in appropriate places, properly ventilated, tap water available and continuously cleaned)\(^6\).
3. **Classroom specification** which includes classroom size (appropriate size means one square meter / student), cleanliness, lighting, windows (should not be at the back or front of the classroom to avoid glare on blackboard), ventilation (either natural through windows, or mechanic using fans, preferably classroom ventilation is by placing 2 open windows on opposite sides of standard size i.e. 1/6 -1/4 of the floor), heating and cooling facility, adequacy of desks, age-appropriate desks (the height of the seat should be proportionate to the length of students leg), blackboard (appropriate blackboard must be dark and not shiny, with a place where chalk particles are deposited and placed in the middle of the wall with a distance of 1.5-2 meter from first desk row), and type of chalk\(^6\).

A separate questionnaire form has been filled in by the investigator for each visited school. Descriptive statistical measures have been used including numbers and percentages for each outcome variable used in assessing physical school environment.

**Results**

In regard to area surrounding the school, study results revealed that 52% of surveyed schools are near main street, 80% of them there was a nearby source of pollution which was solid waste aggregate in 80% of those schools (Table 1).

Table (1): Frequency distribution of surveyed schools according to surrounding area characteristics.

<table>
<thead>
<tr>
<th>Surrounding area parameters</th>
<th>(N=25) No.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Distance from main street</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Close</td>
<td>13</td>
<td>52.0</td>
</tr>
<tr>
<td>Far</td>
<td>12</td>
<td>48.0</td>
</tr>
<tr>
<td>Nearby pollution source</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>20</td>
<td>80.0</td>
</tr>
<tr>
<td>Absent</td>
<td>5</td>
<td>20.0</td>
</tr>
<tr>
<td>Source of pollution</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Garbage</td>
<td>20</td>
<td>80.0</td>
</tr>
<tr>
<td>Stagnated water</td>
<td>8</td>
<td>32.0</td>
</tr>
<tr>
<td>Noise</td>
<td>6</td>
<td>24.0</td>
</tr>
<tr>
<td>Bucher shops</td>
<td>5</td>
<td>20.0</td>
</tr>
<tr>
<td>Industrial</td>
<td>1</td>
<td>4.0</td>
</tr>
</tbody>
</table>

Regarding school environment the study revealed that 76% of surveyed schools have a standard wall, 80% of school yards are proportionate with the number of student, 56% of schools gardens are lacking maintenance while 24% of schools found without gardens and 28% of schools have in-proper cleanliness, 60% of schools found having only a general source of electricity while only 40% of schools having both general and local sources for electricity (Table 2).

Regarding environmental sanitation parameters; 12% of schools found without garbage containers, 80% of schools found lacking a daily disposal of waste, 40% of schools do not check the chlorine amount in their drinking water, 72% of schools having inadequate faucets and 44% of them are non-standard. 92% of schools founds having insufficient number of toilets and 76% of them having poor sanitary condition (Table 3).

Regarding classroom specifications study results revealed that 80% of classrooms are inappropriate to number of students, 48% of them have inadequate lighting & 28% of them have poor ventilation, 20% of them have inadequate cleanliness, 28% of them having inadequate number and partially appropriate desks. On the other hand 52% of blackboards were found to be appropriate, and 96% of chalk was oily (Table 4).

Table (2): Frequency distribution of surveyed schools in regard to building characteristics.

<table>
<thead>
<tr>
<th>School building parameters</th>
<th>(N=25) No.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>School wall height</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standard</td>
<td>19</td>
<td>76.0</td>
</tr>
<tr>
<td>Not-standard</td>
<td>6</td>
<td>24.0</td>
</tr>
<tr>
<td>School yard proportionate with no. of students</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proportionate</td>
<td>20</td>
<td>80.0</td>
</tr>
<tr>
<td>Not proportionate</td>
<td>5</td>
<td>20.0</td>
</tr>
<tr>
<td>School garden</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>19</td>
<td>76.0</td>
</tr>
<tr>
<td>Absent</td>
<td>6</td>
<td>24.0</td>
</tr>
<tr>
<td>Garden maintenance</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maintained</td>
<td>5</td>
<td>26.3</td>
</tr>
<tr>
<td>Unmaintained</td>
<td>14</td>
<td>73.7</td>
</tr>
<tr>
<td>School cleanliness</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clean</td>
<td>18</td>
<td>72.0</td>
</tr>
<tr>
<td>Not clean</td>
<td>7</td>
<td>28.0</td>
</tr>
<tr>
<td>Source of electricity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>General only</td>
<td>15</td>
<td>60.0</td>
</tr>
<tr>
<td>General and local</td>
<td>10</td>
<td>40.0</td>
</tr>
</tbody>
</table>
Table (3): Frequency distribution of studied schools according to environmental sanitation parameters.

<table>
<thead>
<tr>
<th>Environmental sanitation parameters</th>
<th>N=25</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presence of garbage container</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>22</td>
<td>88.0</td>
</tr>
<tr>
<td>Absent</td>
<td>3</td>
<td>12.0</td>
</tr>
<tr>
<td>Type of garbage container</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standard</td>
<td>10</td>
<td>40.0</td>
</tr>
<tr>
<td>Not standard</td>
<td>12</td>
<td>48.0</td>
</tr>
<tr>
<td>Daily disposal of waste</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>5</td>
<td>20.0</td>
</tr>
<tr>
<td>absent</td>
<td>20</td>
<td>80.0</td>
</tr>
<tr>
<td>Chlorine amount checking</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>15</td>
<td>60.0</td>
</tr>
<tr>
<td>Absent</td>
<td>10</td>
<td>40.0</td>
</tr>
<tr>
<td>Number of faucets</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adequate</td>
<td>18</td>
<td>72.0</td>
</tr>
<tr>
<td>Inadequate</td>
<td>7</td>
<td>28.0</td>
</tr>
<tr>
<td>Faucets state</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standard</td>
<td>14</td>
<td>56.0</td>
</tr>
<tr>
<td>Not standard</td>
<td>11</td>
<td>44.0</td>
</tr>
<tr>
<td>Number of toilets</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adequate</td>
<td>2</td>
<td>8.0</td>
</tr>
<tr>
<td>Inadequate</td>
<td>23</td>
<td>92.0</td>
</tr>
<tr>
<td>Toilet sanitation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acceptable</td>
<td>6</td>
<td>24.0</td>
</tr>
<tr>
<td>Unacceptable</td>
<td>19</td>
<td>76.0</td>
</tr>
</tbody>
</table>

Table (4): Frequency distribution of studied schools according to classroom specification parameters.

<table>
<thead>
<tr>
<th>Classroom specification parameters</th>
<th>N=25</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Classroom size in proportion to number of students</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proper</td>
<td>5</td>
<td>20.0</td>
</tr>
<tr>
<td>improper</td>
<td>20</td>
<td>80.0</td>
</tr>
<tr>
<td>Lighting</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adequate</td>
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<tr>
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</tbody>
</table>

Discussion

Being more than 50% of surveyed schools near a main street, this can reflect the high possibility of noise pollution and the higher risk of getting accidents and/or hazardous effect upon students health and learning abilities among such schools. Such result go with the findings of a similar study conducted at Al-Muthanna Governorate in Iraq during the year 2008. However a nearby pollution source was present in 80% of surveyed schools which is mainly garbage collections, in comparison to only 20% of schools in Baghdad/ Al-Karkh, such point looks to be a very dangerous in regard to communicable diseases transmission and respiratory problems occurrence among both students and teaching staff of Mosul schools. Such high rate can reflect the poor services introduced by Ministry of Municipalities and poor supervision activities of Ministry of Environment in Mosul city.

In regard to school cleanliness, 72% of surveyed schools found to be acceptable. Such result is nearly equal to the findings of a similar study conducted in Baghdad /Al-Rusafa. From other point of view, majority of school gardens found to be unmaintained in comparison to only 30.8% of schools through a similar study in Sulaymaniyah/Iraq. This can reflect the poor monitoring and health educational role of administrative staff of such schools in maintaining a healthy school environment.

Regarding safe water supply, 72% of surveyed schools, found having inadequate faucets and 92% have inadequate toilets (76% of them have poor sanitation). Such high rates go with the findings of a similar study conducted in Mesan Governorate/Iraq and with the Dubai International Humanitarian Aid and Development report more than half of primary schools in developing countries have no adequate water facilities and nearly two thirds lack adequate sanitation. It reflect the highly neglected school health supervision services.

Discussing classroom specifications, 80% of classrooms found with improper size in comparison to 20% only in Basra/Iraq; and 48% of blackboards are inappropriate. Such
high rate can express the stressful classroom conditions and one of the difficult learning environmental problems which might affect students' school performance in addition to their ill-health effect in regard to proper vision and respiratory health of students. The wellbeing of such student is very important because primary school age children constitute 16.3% of the total Iraqi population. On the other hand 80% of visited classrooms were clean which is better than that of Baghdad /Al-Karkh which 61.5% (6). From other point of view, although the study has been conducted during winter, no any heating facility found available among visited classrooms. Such point can expose school children to a lot of cold months respiratory health problems and increase the risk of school absenteeism.

Conclusions
The present study concluded that the primary schools in Mosul city found to have a number of improper physical environmental conditions. 52% of visited schools found to be constructed near a main street, 80% of them have a nearby source of pollution, 72% of them have inadequate faucets, 92% have inadequate toilets, 76% of toilets found lacking proper sanitation and 80% of classrooms found with inappropriate size in regard to number of students.

The present study recommended the improving environmental conditions around the schools need a proper coordinated activities between the Ministries of Education, Environment and Municipalities. Furthermore improving primary schools infrastructures (faucets, toilets and sanitation). Lastly number of students in each classroom must be proportionate to its size and availability of air conditioning facilities.

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Opportunistic fungi in lower respiratory tract infection among immunocompromised and immunocompetent patients

Manahil M. Yehia, Zainalabideen A. Abdulla
Department of Microbiology, College of Medicine, University of Mosul.

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ABSTRACT

Objectives: (1) to identify the opportunistic fungi from sputum and bronchial wash of patients with lower respiratory tract (LRT) infections in immunocompromised (IC) and immunocompetent (IP) patients, and apparently healthy controls, (2) to detect antibodies against Aspergillus species by double immunodiffusion test (ID).

Subjects and methods: Three hundred patients suffering from LRT infections of both IC (150/300) and IP (150/300) patients were included in the study. The clinical specimens collected were samples of sputum (247), bronchial wash (80), and blood (300). The control group was 50 apparently healthy individuals, from whom sputum and blood were obtained. The identification of the isolated fungi was carried out by direct fluorescent and/or light microscopy, culture on different media, and biochemical tests. Moreover, the serums of patients with Aspergillus isolates were tested by double ID test for the detection of specific antibody.

Results: One hundred eighty patients showed fungal elements in their clinical specimens (60%). Two hundred four funguses were detected, including 24 samples with 2 types of isolates. The identified fungi were encountered from both IC (60.9%) and IP (39.1%) patients with a significant difference between them (p< 0.001). Nine opportunistic genus-species were identified. Five were filamentous type namely Aspergillus spp., Penicillium spp., Cladosporium spp., Fusarium spp., and Geotrichum spp. while the other 4 were unicellular organisms including Candida spp., Saccharomyces cerevisiae, Cryptococcus neoformans, and Rhodotorula rubra. In the control group, 36% showed fungal isolates in their sputa, and the ID test showed a positive result for antibody in only one patient with Aspergillus isolate.

Conclusions: Many opportunistic fungi are important uncommon pathogens in LRT infections in IC patients. The ID test is of limited value for the detection of specific antibody of Aspergillus spp.

Keywords: Opportunistic fungi, fungi in L.R.T.
Aspergillus spp. The pathogenicity is low and primary aspergillosis rarely occurs in man (2). Aspergillosis is one of the earliest fungal diseases recognized and the major portal of entry for infection is the respiratory tract. Nosocomial infection may be associated with dust exposure during building renovation or construction. The most important nosocomial infection due to the Aspergillus species is pneumonia (4).

Cryptococcus neoformans. The organism exists as a yeast in both nature and tissue. It is 4-6 μm in diameter, with a capsule. Pulmonary infection with C. neoformans may have several untoward clinical sequelae (7). Most of them are viewed as being "clinically silent" (10), but symptommatic disease can occur. Pulmonary cryptococcosis is rare in the immunocompetent individuals (11), or may be asymptomatic and resolve spontaneously. The disease commonly occurs in AIDS. It occurs also in those, who on cytotoxic chemotherapy, those receiving corticosteroids or patients with hematological malignancy (12).

A group of rare yeasts, which are normally non pathogenic or with low virulence, and considered as occasional part of normal flora specially species of Exophilia, Phialophora, Bipolaris, Cladosporium and Alternaria (6).

Candida are small yeasts that reproduce by budding. There are more than 150 species of Candida, about 10 of them cause diseases in human (8). The main species is Candida albicans, and the others are C. tropicalis, C. krusei, C. parapsilosis (7). Candida species are normal commensals of human. They produce a wide variety of infections, and distinguishing between colonization and infection can sometime be a challenge (8). They are the most common cause of opportunistic mycoses worldwide. Candida pneumonia is one of the most challenging of all the candida infection.

Penicillium, Aspergillus, Candida spp. and primary aspergillosis rarely occurs in man (2). Aspergillosis is one of the earliest fungal diseases recognized and the major portal of entry for infection is the respiratory tract. Nosocomial infection may be associated with dust exposure during building renovation or construction. The most important nosocomial infection due to the Aspergillus species is pneumonia (4).

Hyalohyphomycetes are unusual hyaline fungal pathogens cause hyalohyphomycosis, where the tissue morphology of the causative organism is mycelial. The etiological agents include species of Penicillium, Paecilomyces, Acremonium, Fusarium, and Scopulariopsis (6).

Phaehomyphomycetes are fungi with dark-walled septated hyphae and sometimes yeast or a combination of both forms in tissue that cause phaeohyphomycosis. These fungi include various dematiaceous hyphomycetes...
in sputum, urine and stool (6). The main genera of these yeasts are *Trichosporon*, *Rhodotorulla*, and *Saccharomyces*. The infections caused are opportunistic and occur in patients with altered host defense (13).

Hence, the main aim of the present study is to identify the opportunistic fungi isolated from immunocompromised and immunocompetent patients with LRT infections.

**Subjects and methods**

**Patients:** Three hundred patients with lower respiratory tract (LRT) infection were included in this study that extended from April 2007 to June 2008. The males were 175 (58.3%) and females were 125 (41.7%). The age of the patients ranged from 1-89 (mean ± SD = 55.44 ± 17.9) years. The patients were either immunocompromised (IC) or immunocompetent (IP) with equal number, 150 (50%) for each group.

The immunocompromised patients had the following primary or underlying diseases:
1. Different types of carcinoma and leukemia: 69/150 (46%).
2. Uncontrolled diabetes mellitus of >5 years duration: 38/150 (25.3%).
3. Old tuberculous patients (Negative AFB at the time of the study): 16/150 (10.7%).
4. Chronic diseases under long – term corticosteroids therapy: 27/150 (18%).

**Normal control:** Fifty apparently healthy individuals were enrolled in the current study as a control group. They were 28 (56%) males and 22 (44%) females. Their ages ranged between 15-60 (mean ± SD = 36.1 ± 12.3) years. These individuals were 20 hospital workers, 10 medical staff, 10 patients’ companions, and 10 individuals from the general population visiting the hospitals.

**Studied samples:** A total of 627 samples were collected from patients in Teaching Hospitals (RCU, Bronchoscopy Unit and Wards). The samples consisted of 247 sputum and 80 bronchial wash (27 patients with both sputum and bronchial wash at the same time). Three hundred samples of blood obtained from all patients. From the 50 control individuals, both sputum and blood samples were also obtained and processed in the same manner as for patients.

The sputum of each patient was shaken, by a vortex for 3-5 minutes for homogenization. The B. wash was centrifuged for 5 minutes, then the sediment was used for culture and direct examination. The blood was centrifuged for 3 minutes then the serum stored at -20°C until use.

**Isolation of the fungi**

The clinical specimens (B. wash and/or sputum) of the patients and sputum of control individuals were inoculated onto brain heart infusion (BHI) blood agar and double plates of modified Sabouraud’s agar with antibiotics then incubated at 28-30°C for several days (14). The cultures were examined daily after the third day of incubation, if no growth was obtained after 2 weeks, it was considered negative and discarded.

**Direct examination**

Four slides were prepared from each clinical specimen. Two wet mounted slides, one with 20% KOH solution and the second with 20% KOH and calcofluor solution, then examined under 40X of light and fluorescent microscopes respectively (14). The third heat fixed smear was stained by Gram’s method and examined under oil immersion lens, and the last slide was nigrosine stained smear.

**Identification of the isolates**

Biochemical tests (API-C, urease), germ tube test, morphology on cornmeal agar Tween 80, slide culture technique and growth and characteristics on Czapek's agar were used for identification of yeasts and molds.

Double immunodiffusion technique (Ouchterlony) was used to test the presence of antibody in serum of patients with *Aspergillus* isolates against antigen (15). The *Aspergillus* antigens and anti-*Aspergillus* antibody used were from Meridian, Bioscience, Inc. Cincinnati, Ohio with Cat. No. 100501 and 100901 respectively.

The data were analyzed statistically as follows:
1. Standard statistical methods were used to describe the results of the study: mean,
standard deviation, number and percentage.
2. Observed / expected $\chi^2$ square was used to find the differences between the percentages.
The statistical results considered significant at $p<0.05$.

**Results**
Among the 300 cases studied, a total of 204 opportunistic fungi were detected from IC (124) and IP (80) patients (Table 1). There was a significant difference ($P<0.001$) between the number of fungal isolates encountered in IC and IP patients.
Out of the 50 control individuals, 18 (36%) showed positive results for opportunistic unicellular fungi only. The isolates obtained from their sputum were 14 (28%) $C.\ albicans$, 2 (4%) $S.\ cereviciae$, and 2 (4%) unidentified Candida species.

**Opportunistic (monomorphic) molds**

**Aspergillus**
Four species of the genus Aspergillus were detected from the clinical specimens. The total isolates were 12, five of them were $A.\ flavus$, 3 $A.\ fumigatus$, 3 $A.\ niger$, and 1 $A.\ terreus$. The number and percentage of the isolates from both IC and IP and the types of clinical specimens from which Aspergilli were isolated are shown in table 2.

Identification of Aspergilli done by direct microscopical examination of the clinical specimens by different staining methods in addition to the culture, slide culture technique and growth on Czapek’s agar.

Ouchterlony (ID) test detected the Aspergillus antibody in serum of one patient out of the 12 with Aspergillus isolates in comparison to the control (Fig.1). Serum of 33 normal controls, and 33 cases of confirmed Aspergillus negative results were tested in the same manner for specific antibodies against Aspergillus antigens, and all showed negative results.

**Miscellaneous opportunistic molds**
Ten isolates of the filamentous fungi were detected. They were 4 (1.9%) Penicillium, 3 (1.5%) Cladosporium, 2 (1%) Fusarium, and 1 (0.5%) Geotrichum (Table 1). The identification depended on the direct microscopical appearance of oval cells and fragments of mycelial elements by different staining methods, in addition to the culture on different media for the colonial morphology and microscopy.

### Table (1): The multicellular and unicellular opportunistic fungi isolated from patients.

<table>
<thead>
<tr>
<th>Fungi</th>
<th>Multicellular (no.=150)</th>
<th>Immunocompromised (no.=150)</th>
<th>Total</th>
<th>No.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>%</td>
<td>%</td>
<td></td>
<td>No.</td>
<td>No.</td>
</tr>
<tr>
<td><strong>MULTICELLULAR</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.0</td>
<td>2</td>
<td>4.9</td>
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<tr>
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<td>2</td>
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<tr>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0.5</td>
<td>1</td>
<td>1</td>
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<tr>
<td><strong>UNICELLULAR</strong></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>37.3</td>
<td>76</td>
<td>51.8</td>
<td>106</td>
<td>89.2</td>
<td>182</td>
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<tr>
<td>35.3</td>
<td>72</td>
<td>47.6</td>
<td>97</td>
<td>82.8</td>
<td>169</td>
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<tr>
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<td>1.9</td>
<td>4</td>
<td>3.4</td>
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<tr>
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<td>1</td>
<td>1.9</td>
<td>4</td>
<td>2.5</td>
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<td>39.3</td>
<td>80</td>
<td>60.7</td>
<td>124</td>
<td>100.0</td>
<td>204</td>
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</table>

Significant difference between total No. of opportunistic isolates from immunocompromised and immunocomponent patients according to Chi-square test ($p<0.001$).
Table (2): The number and percentage of opportunistic fungi isolated from clinical specimens in both IC and IP patients.

<table>
<thead>
<tr>
<th>Isolates</th>
<th>Immunocompetent</th>
<th>Immunocompromised</th>
<th>Total</th>
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</thead>
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<tr>
<td></td>
<td>B. wash</td>
<td>Sputum</td>
<td>B. wash</td>
</tr>
<tr>
<td>Candida spp.</td>
<td>7.8</td>
<td>16</td>
<td>30</td>
</tr>
<tr>
<td>Aspergillus spp.</td>
<td>2.0</td>
<td>4</td>
<td>6.5</td>
</tr>
<tr>
<td>S. cerevisiae</td>
<td>0.5</td>
<td>1</td>
<td>1.5</td>
</tr>
<tr>
<td>C. neoformans</td>
<td>0.5</td>
<td>1</td>
<td>1.5</td>
</tr>
<tr>
<td>Penicillium spp.</td>
<td>1.0</td>
<td>2</td>
<td>0.5</td>
</tr>
<tr>
<td>Cladosporium spp.</td>
<td>0.5</td>
<td>1</td>
<td>0.5</td>
</tr>
<tr>
<td>Fusarium spp.</td>
<td>0.5</td>
<td>1</td>
<td>0.5</td>
</tr>
<tr>
<td>Geotrichum spp.</td>
<td>0.5</td>
<td>1</td>
<td>0.5</td>
</tr>
<tr>
<td>R. rubra</td>
<td>17 (8.3%)</td>
<td>9.8</td>
<td>20</td>
</tr>
</tbody>
</table>

* i.c = immunocompromised, i.p = immunocompetent.

**Opportunistic unicellular fungi**

The total number of yeasts isolated from cases of LRT infections was 182 (89.2%). These isolates belong to 4 genera namely Genus Candida, Cryptococcus, Saccharomyces and Rhodotorula (Table 1).

**Genus Candida**

The 169 (82.8%) isolates of this genus were categorized as C. albicans (129/169, 76.3%), C. tropicalis (14/169, 8.3%), C. krusei (5/169, 3%) and 21/169 (12.4%) were unidentified Candida species. The frequency of the isolated Candida species from IC were 47.6% in comparison to 35.3% in the IP ones (Table 1). The relation of Candida isolates to the clinical diagnosis showed that the higher percentages of Candida species were obtained from cases of pneumonia.

Different tests were used to identify the species of the 169 isolates including direct examination of the clinical specimens with different stains, and culture on different media. Additional identification tests namely germ tube, chlamydospore, and API-C system were also used.

**Genus Saccharomyces**

Seven isolates (3.4%) of the genus Saccharomyces were detected from both IC...
Saccharomyces grew well on modified Sabouraud's agar, and all the 7 isolates were identified as *S. cerevisiae* by API-C system.

**Genus Rhodotorula**

One isolate (0.5%) was obtained from the sputum of an IC patient (Table 2) with pneumonia. The isolate gave positive urease test and identified as *R. rubra* by API-C system.

**Genus Cryptococcus**

Five *Cryptococcus* isolates (2.5%) were detected from 4 IC and 1 IP patients (Table 1). For the identification, the appearance of the capsule in direct examination of the clinical specimen stained with nigrosine. Colonies grow well on BHI blood agar, in addition to their growth on modified Sabouraud's agar at 28°C, the isolates gave positive urease test and grew well at 37°C. All the detected Cryptococci were identified as *C. neoformans* by API-C system.

**Discussion**

It is not easy to determine the pathogenic role of fungal isolates from the respiratory tract, i.e., to differentiate between infections, colonization and contamination (16). However, the prevalence and prognosis of pulmonary fungal infection has been difficult to evaluate since diagnosis was seldom confirmed (17). A significant difference (p< 0.001) was recorded in this study between the opportunistic isolates from IC and IP patients. An important factor contributing to the increasing incidence of infection by fungi that have not been previously described to be pathogenic, is the rise in numbers of IC patients who are susceptible hosts for the most uncommon microbial agents (2).

In order to validate the results of fungal isolation from patients, a similar identification process was carried out on the 50 individuals of the control group. It was found that all the fungi isolated were of opportunistic yeasts including *C. albicans* (14%), *S. cerevisiae* (2%), and unidentified *Candida* species (2%). This may throw light on the possibility of real LRT infections caused by the fungi isolated from patients.

Twelve patients showed *Aspergillus* isolates (5.9%). Those patients were predominantly males (11/12). This is in keeping with other studies that reported infection occurs in males more than females (18). *Aspergillus* isolates were encountered more (10/12) in IC than IP group of patients. Since *Aspergillus* is an opportunistic fungus, the IC patients are more susceptible for its colonization. Whether infection (aspergillosis) could happen, it is a matter of balance between the immunity of the person versus the pathogenicity of the organism. Denning and Coworker (19) mentioned that pulmonary aspergillosis depends upon the immune status of the patients. Airway colonization without evidence of tissue invasion can be found in chronic obstructive pulmonary disease patients, smokers, and even healthy individuals (20).

The first step in the evaluation of clinical specimens during this work is mounting in 20% KOH solution with or without calcofluor stain, and Gram's stain which are useful to assess the suitability of specimens for further processing and interpretation. Out of the 12 positive isolates of Aspergillus, 8 of them showed branching septate hyphae in the sputum, bronchial wash or both of them. Ellis (21) reported that the presence of the hyaline, branching septate hyphae consistent with *Aspergillus* in any specimen from a patient with supporting clinical symptoms should be considered significant, but is not a specific identification of the causative agent. Immunodiffusion test showed positive line of precipitation for antibody in one case with *Aspergillus* isolate, while negative for antibody in the normal and case control groups. This test has proven to be of value in the diagnosis of aspergilloma and invasive aspergillosis. However, it should never be used alone, and must be correlated with other clinical and diagnostic data (21).

The hyalohyphomycetes are rarely encountered in clinical specimens and rarely cause infection. Seven isolates of this group were identified during the study. All were obtained from IC patients with prolonged neutropenia, especially in leukemic patients, corticosteroid therapy, and cytotoxic
chemotherapy. It was reported that the infection was more frequent in patients with acute leukemia (56%) and most patients (83%) were neutropenic at diagnosis (22).

The one isolate of phaeohyphomycetes, namely Cladosporium was identified from 3 cases. The characteristic brown pigmented branching septate hyphae were detected in the clinical specimens in direct KOH and calcofluor mount, in addition to the culture. Clancy and Co-workers (23) reported that phaeohyphomycosis caused by brown-pigmented fungi where the tissue morphology of the causative organism are mycelia.

During recent years, a high incidence of yeast infection has been reported (24). In the present study, members of the 4 genera (Candida, Cryptococcus, Saccharomyces, and Rhodotorula) were identified from the clinical specimens. One hundred sixty nine (82.8%) isolates of Candida species were obtained. A significant higher percentage of Candida isolates (47.6%) were detected in IC in comparison to 35.5% in IP patients. Out of the 50 individuals included in this study as a control group, 16 (34%) of them showed Candida species in their sputa (14; 32% C. albicans and 2 (4%) unidentified Candida species. Nicod and Co-workers (9) mentioned that a small number of Candida species are normally present in healthy persons, but increased when the normal microbial flora is altered by antibiotics or when there is a defect in immunocompetence. In this work, C. albicans (76.3%) is the main isolate in comparison to C. tropicalis (8.3%) and C. krusei (3%), in addition to 12.4% unidentified Candida species. Jaffer (18) in Babylon province reported that C. albicans (69.2%) was the most common isolate in a study of pulmonary fungal infection, less frequency are C. tropicalis (19.2%), C. kefyr (7.6%) and C. krusei (3%).

One hundred twenty nine isolates of C. albicans reported in this study were identified by the production of germ tube and formation of chlamydospore except 4 isolates showed negative germ tube production and identified by API-C system as the other non albican candida species. Germ tube and chlamydospore formation test were used for the identification of more than 90% of C. albicans (6).

Cryptococcus identified in this study represent 2.3% of the isolates. Among the 5 patients with Cryptococcus isolates, 4 of them from IC. This illustrates that colonization or infection occurs predominantly in such patients. Furthermore, patients with pneumonia showed most of the Cryptococcus isolates (3/5). In a previous report, it was mentioned that Cryptococcus causes primarily pulmonary pneumonia then disseminates to other organs mainly the brain and meninges in IC patients (25). The identification of Cryptococcus depends on the presence of capsule, growth on BHI blood agar at 28°C and positive urease test, then identified to species level by API-C system. The demonstration of encapsulated yeast cells by nigrosine in sputum specimens should be considered significant for Cryptococcus (24).

Saccharomyces has been reported rarely as a cause of opportunistic infection. Saccharomyces cerevisiae which is identified by API-C system during the study, accounted for 3.4% of all the isolated fungi. Kiehen and colleagues (26) reported that Saccharomyces cerevisiae accounted for less than 1% of all yeast infections isolated at a cancer hospital and mostly isolated from the respiratory tract. Saccharomyces cerevisiae constitute part of the normal or transient flora of the throat (27) and from the control group of this study 2/50 (4%) individuals showed Saccharomyces cerevisiae in their sputum.

The Rhodotorula may colonize humans, but may infect individuals with predisposing risk factors. One isolate of this yeast was detected from sputum of IC patient, and identified as R. rubra by API-C system. Tuon and Costa mentioned that Rhodotorula was previously considered non-pathogenic, but during the last decades, it has emerged as an opportunistic etiologic agent particularly in IC patients (28).

References


Identification and treatment of a patient with pneumocystis pneumonia (case report)

Manahil M. Yehia*, Dhaher J. S. Al-Habbo**, Zainalabideen A. Abdulla*
* Department of Microbiology; ** Department of Medicine, College of Medicine, University of Mosul.

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ABSTRACT

A case of pneumocystis pneumonia was diagnosed on clinical and mycological grounds. A 35 - year - old man was presented with severe chest infection. His medical history included lymphoma for 5 years and under treatment with cytotoxic drugs. The patient diagnosed as a case of pneumonia and treated with antibiotics for one week but with no response. Later on, his sputum was sent for mycological examination that revealed the cysts and trophic forms of pneumocystis jirovecii. Good response with complete healing was achieved after 3 weeks of treatment with co-trimoxazole. Pneumocystis pneumonia may be suspected clinically in hospitalized patients, but this is the first case to be confirmed mycologically in Mosul. Good awareness of the full clinical spectrum of the disease aided by mycological study is needed to minimize the misdiagnosis of cases.

Keywords: Pneumocystis jirovecii, pneumocystis pneumonia, pneumocystosis.

Pneumocystis pneumonia (PCP) is caused by a yeast-like fungus, pneumocystis jirovecii. This type of pneumonia is a condition that could be successfully treatable if diagnosed early (1). The causative agent first described as a protozoan and reclassified as a fungus in 1988 (2). Delanes named the organism in honor Dr. Carini after isolating it from infected rats. Years later, Dr. Otto Jirovec and his group isolated the organism from human, and the organism responsible for PCP was renamed as pneumocystis jirovecii, which is human specific (3, 4).

The disease is relatively rare in normal people although the fungus present among the general population (5), but it is commonly...
encountered in immunocompromised patients \(^{(6)}\). The patient who have PCP without AIDS typically present with an abrupt onset of respiratory insufficiency that may correlate with an increased dosage of immunosuppressant medication \(^{(7)}\). Extra-pulmonary involvement is rare and systemic spread to many organs as liver, spleen and lymph nodes can result in severe disease refractory to standard therapeutic regimen \(^{(8)}\).

The causative organism establishes latency in immunocompetent individuals. Immunosuppression especially of the T-cell function leads to reactivation of infection resulting in disease \(^{(1)}\). The common symptoms of PCP include shortness of breath, low grade fever, non-productive cough and usually no large amount of sputum unless the patient has an additional bacterial infection \(^{(2)}\).

The approach to the diagnosis of PCP and its treatment remains controversial. Because of the critical condition of the patients, some authors advocate the use of clinical criteria alone in the diagnosis of \(P. jirovecii\), however, it has become increasingly clear that such an empiric regimen may be associated with an overall worse outcome for the patient \(^{(9)}\).

The commonly used medication is a combination of trimethoprim and sulfamethoxazole (TMP-SMX), but some patients with known allergies to sulfa cannot tolerate this therapy. Other medications that are used include dapsone, trimetrexate and clindamycin. For prophylaxis against \(P. jirovecii\) in immunocompromised patients, cotrimoxazole, dapsone/pyrimethamine, or pentamidine nebulizer can be used \(^{(2)}\).

**Case report**

A 35-year-old man was admitted to the Respiratory Care Unit (RCU) in Ibn-Sina Teaching Hospital referred from the oncology unit with severe chest infection. He had nausea, malaise, fever of 37.6°C, dyspnea, dry cough to start with, then the patient started to have productive cough with white sputum and then haemoptysis for several days. His medical past history included lymphoma for 5 years and he was under regular treatment with courses of cytotoxic drugs. Radiological examination showed diffuse infiltrates in both lungs and was diagnosed as a case of broncho pneumonia. The blood picture showed: Hb 92 g/L; PCV 33%; total WBC 11.4×10\(^9\) L (N 59%, L 38%, M 3%) and ESR 110 mm/hr. The patient first was treated in the oncology unit with ampicilin-cloxacillin and ceftriaxone for nearly one week but with no response and then referred to the RCU.

The diagnosis of the present case as PCP was made on the bases of chest x-ray findings and clinical examination, with the exclusion of other possible causes and was treated accordingly with TMP-SMX. At the same time, the early morning sputum from the patient was sent to the Department of Microbiology, College of Medicine, University of Mosul, for laboratory confirmation.

**Laboratory report:** The whitish bloody sputum was subjected to direct microscopical examination of stained slides with Giemsa and Touludin blue O stains. The trophic forms and cysts of \(pneumocystis jirovecii\) were revealed by these stains respectively (Figure I- b & c). In addition, other wet mounted slide with 20% KOH solution and calcofluor stain showed the cysts of the fungus when examined under fluorescent microscope (Figure I- a).

**Treatment:** The patient was started on TMP-SMX (120 mg/kg p.o) in 4 divided doses. Because the pneumonia was severe, intravenous hydrocortisone 100 mg 4 times daily was added. The treatment was continued for 3 weeks, with full recovery of the patient.
Figure (I): *Pneumocystis jirovecii* seen in sputum:
A. 20% KOH and calcofluor stain showing the spherical cyst (cyst wall and thickening intensely flurescent) by fluorescent microscopy (40X).
B. Giemsa stained smear showing intracystic bodies (short arrowed), 100X, and extracellular, trophozoites (long arrowed), 100X.
C. Toludine blue stained smear showing many spherical violet cysts (arrowed), 100X.

Discussion
Pneumocystis pneumonia is usually considered as a secondary infection in immunocompromised patients. It remains the most prevalent opportunistic infection in patients infected with the immunodeficiency virus (10). The number of patients who are receiving chronic immunosuppressive medication or who have an altered immune system and are thus at risk for PCP is rapidly growing (2). The studied patient had lymphoma and under cytotoxic therapy for 5 years presented with severe pneumonia in the RCU. The PCP is an increasing common infection in cancer patients, such as those with lymphoma and leukemia (11). The development of worsening pneumonia with respiratory failure in patients with hypoxaemia is the most common reason for admission to an intensive care unit (2).

In hospitalized patients, the clinicians depend on the clinical diagnosis of PCP and start treatment empirically. The diagnosis of such an infection requires the identification of the organism from the clinical specimens microscopically (12), because until now the organism cannot be propagated in culture (13). This had confirmed the clinical interpretation and treatment were continued. The diagnosis of the reported patient was confirmed as a case of PCP by the detection of the trophic forms and cysts of *P. jirovecii* in his sputum. This is the first patient confirmed to have PCP and to be reported in Mosul, by utilizing the different staining methods. The patient was treated with co-trimoxazole with a good clinical response, complete healing was achieved after 3 weeks of treatment.

In conclusion, Pneumocystis pneumonia can be diagnosed by clinical interpretation and confirmed by the laboratory identification of the causative agent.

References
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عميد الجماعة

 yabani@yandex.com

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Email: annalsmosul@yahoo.com

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