HUMAN PARVOVIRUS B19 INFECTION: ITS ROLE IN ACUTE ARTHROPATHIES

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KEY WORDS: HUMAN PARVOVIRUS, ACUTE ARTHROPATHIES.

ABSTRACT

Introduction: Viral infections have a number of important effects on the immune system. Infection with human parvovirus B19 (B19) has a diverse range of clinical manifestations including erythema infectiosum, polyarthropathy, transient aplastic crisis, hydrops fetalis and fetal death as well as chronic infection and anemia in immunocompromised hosts.

Since its discovery in 1975, it has been noted that HPV B19 frequently causes a self-limiting polyarthritis in adults. It has also been debated whether, in some patients, B19 may act as a trigger for RA.

Objective: The aim was to determine the incidence and significance of antibodies to the parvovirus B19, we detected the presence of B19 IgM and IgG antibodies in 40 rheumatoid arthritis (RA) patients, 10 SLE patients, 10 osteoarthritis patients and 30 normal adults.

Results: B19 IgM was positive in 60% of RA patients. This rate was significantly higher than the control group. They were mostly females (70%), duration of illness was 3 months to one year (68.7%) with polyarthritis, large and small joints were more affected (72.7%) with manifestations of acute inflammation. Rheumatoid factor (RF) was negative in 70% of them. Regarding osteoarthritis patients, B19 IgM antibodies were detected in 40% of them. They were females (60%) with polyarthritis, large and small joints were more affected (75%). On the other hand B19 IgM antibodies were not detected in SLE patients or in the control group.
**Conclusion:** Parvovirus B19 is important viral agent causing joint manifestations and should be considered in the differential diagnosis of acute arthropathy in adults, as early treatment of these cases results in fewer complications.

**INTRODUCTION**

Human parvovirus B19 (B19) is an unenveloped single stranded DNA virus (5.5 kb) There are two capsid proteins of approximately 83 and 60 kDa. B19 is resistant to lipid solvents and is relatively sensitive to acid and alkali and to heat denaturation. Spread is by the respiratory route (Chevrel et al., 2000).

B19 was first discovered in blood donors in 1975 and has been identified as the causative agent of erythema infectiosum, an acute exanthema of childhood. In adults, particularly women, the rash is less frequent, but there may be involvement of joints leading to acute arthritis. It frequently causes a self-limiting non-destructive arthritis in infected adults. The duration of joint affection varies between a few days of arthralgia to months or even years of persistent arthritis (Nesher & Moore, 1997). But progression to erosive rheumatoid arthritis (RA) was reported (Tyndall et al., 1994).

Approximately one week after exposure, an intense viremia develops, which is associated with flu-like symptoms. The viremia lasts several days and is followed by an IgM response, which is detected 10-12 days after exposure. An IgG response develops approximately 2 weeks after exposure. The IgM may persist for several months, and the IgG probably persists for life. Life long immunity most likely occurs after infection, even though IgG levels may drop (Fields, 1996).

In people with B19 infection, HLA-DRB1*04 alleles might increase susceptibility to develop arthritis or in those with arthritis to have persistent disease (Harrison et al., 1998).

B19 was found to invade joints and viral DNA has been detected in the synovial fluid of patients with polyarthralgia (Takahashi et al., 1998). A large numbers of techniques have been used to diagnose B19 infection, and it has been debated whether a possible link between B19 infection and RA could be confirmed if more sensitive methods of detection such as polymerase chain reaction (PCR) were used (Harrison et al., 1998). B19 DNA detection, using PCR technique, was found in 75% of synovial biopsies of patients with RA as compared with only 16.7% of non-RA, implicating the virus in RA pathogeneses (Cassinotti et al., 1998).
et al., 2000) reported a case of dermatomyositis associated with the presence of B19 DNA in muscle biopsy.

**SUBJECTS AND METHODS**

All patients were chosen from the Outpatient Clinic of the Rheumatology Unit and the Rheumatology & Rehabilitation Department of Ain Shams University Hospitals. Blood samples were collected from 40 RA patients, 10 systemic lupus erythematosus (SLE) cases and 10 osteo-arthropathy cases. The control group consisted of 30 normal adults. All patients and normal subjects were chosen in the age range of 40-50 years (mean age 43.6 ± 1.4 years old).

All specimens were drawn in clot tubes and allowed to clot for about 30 minutes at room temperature. Sera were obtained by centrifugation and stored at −20°C until tested. Patients with RA and SLE met the respective criteria of the American College of Rheumatology (ACR) (Arnett et al. 1988 and Tan et al., 1982).

All patients and normal subjects were subjected to the following:

- Westergren erythrocyte sedimentation rate (ESR) was measured with the standard methodology (Fischel, 1967).
- The classical RF was determined with LFT (Omega Diagn– UK) and then by Rose-Waaler test (RWT) (Amboceptor from Dade Behring-Germany) according to the method of Ball (1963).
- Hemoglobin levels (Hb) estimated with coulter (Sysmex SF-3000).
- Antinuclear antibodies (ANA) detection was performed with the indirect immunofluorescent assay (IIF) on Hep2 slides provided by Immco diagnostics-USA. The slides were analyzed with the Nikon epifluorescent microscope.
- Detection of human parvovirus B19 IgM and IgG with enzyme linked immunosorbent assay (ELISA), using the Biotrin International parvovirus B19 IgM and IgG (3rd generation) Enzyme immunoassay (New Jersey-USA) according to the manufacture procedures. Samples with mean absorbance reading greater than or equal to cut off value (COV) x 1.1 were considered reactive (positive) for parvovirus B19 IgM or IgG. Samples with mean absorbance reading less than or equal to COV x 0.9 were considered non-reactive (negative).
RESULTS

This study was performed on 60 patients with different arthropathies, mainly RA (40), SLE (10) and osteoarthritis (10). The RA and osteoarthritis patients were selected to have both sexes equally represented. They presented with polyarthritits, pain, tenderness, limitation of movement and morning stiffness and other manifestations of acute inflammation like hotness, redness and swelling (Table 1).

Table 1: Clinical manifestations of the study sample.

<table>
<thead>
<tr>
<th>Manifestation</th>
<th>RA (40)</th>
<th>SLE (10)</th>
<th>OA (10)</th>
<th>Control (30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morning stiffness</td>
<td>38 (95%)</td>
<td>0</td>
<td>9 (90%)</td>
<td>0</td>
</tr>
<tr>
<td>Pain &amp; tenderness</td>
<td>35 (87.5%)</td>
<td>3 (30%)</td>
<td>8 (80%)</td>
<td>0</td>
</tr>
<tr>
<td>Limitation of movement</td>
<td>31 (77.5%)</td>
<td>6 (60%)</td>
<td>10 (100%)</td>
<td>0</td>
</tr>
<tr>
<td>Hotness &amp; Swelling</td>
<td>9 (22.5%)</td>
<td>1 (10%)</td>
<td>3 (30%)</td>
<td>0</td>
</tr>
<tr>
<td>No. Of joints affected</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Polyartthritis</td>
<td>38(95%)</td>
<td>0</td>
<td>3(30%)</td>
<td>0</td>
</tr>
<tr>
<td>Oligoarthritits</td>
<td>2(5%)</td>
<td>10(100%)</td>
<td>7(70%)</td>
<td>0</td>
</tr>
<tr>
<td>Joints affected: S+L</td>
<td>18 (45%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>S only</td>
<td>22 (55%)</td>
<td>0</td>
<td>9 (90%)</td>
<td>0</td>
</tr>
<tr>
<td>L only</td>
<td>0</td>
<td>0</td>
<td>1 (10%)</td>
<td>0</td>
</tr>
</tbody>
</table>

RA: Rheumatoid arthritis       OA: Osteoarthritis
S: Small joints                L: Large joints

Table 2: Levels of ESR, Hb, ANA and incidence of Anti-B19 IgM and IgG in patients with rheumatic diseases and in normal adults.

<table>
<thead>
<tr>
<th></th>
<th>No</th>
<th>ESR Mean±SD</th>
<th>Hb Mean±SD</th>
<th>ANA (%)</th>
<th>Anti-HPV IgM</th>
<th>Anti-HPV IgG</th>
<th>Anti-HPV IgM and IgG</th>
</tr>
</thead>
<tbody>
<tr>
<td>RA</td>
<td>40</td>
<td>45.4±16.2*</td>
<td>11.3±2.1</td>
<td>6 (16%)*</td>
<td>24 (60%)*</td>
<td>12 (30%)*</td>
<td>11 (27.5%)*</td>
</tr>
<tr>
<td>OA</td>
<td>10</td>
<td>18.6±5.3</td>
<td>14.2±1.3</td>
<td>0 (0%)*</td>
<td>4 (40%)*</td>
<td>6 (60%)</td>
<td>2 (20%)*</td>
</tr>
<tr>
<td>SLE</td>
<td>10</td>
<td>62.6±15.2*</td>
<td>11.8±1.3</td>
<td>10 (100%)*</td>
<td>0 (0%)*</td>
<td>4 (40%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Normal adults</td>
<td>30</td>
<td>12.8±3.3</td>
<td>14.6±1.4</td>
<td>0 (0%)*</td>
<td>0 (0%)*</td>
<td>14 (46.7%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

RA: Rheumatoid arthritis; SLE: Systemic lupus erythematosus; OA: Osteoarthritis; HPV: Human parvovirus B19; ANA: Antinuclear antibodies; *: p <0.05; Significant
SLE patients were females with past history of joint pain; four of them had kidney troubles. Among our studied groups, we found that, as regard ESR and Hb levels, RA and SLE showed high significant difference as compared to the control group. Interestingly, ANAs were found in 16% of RA cases and in all cases of SLE (Table 2).

B19 IgM antibodies were detected, in this study, only in cases of RA and osteoarthritis and their presence was statistically significant as compared to the control group (p<0.05). While B19 IgG antibodies were detected in all groups of patients and normal subjects with no statistical significant difference between them (p>0.05). (Table 2)

Table 3: The clinical presentation of RA cases positive and negative for both IgM and IgG B19.

<table>
<thead>
<tr>
<th></th>
<th>No</th>
<th>+Ve IgM (%)</th>
<th>Early RA +ve IgM</th>
<th>Late RA +ve IgM</th>
<th>Early RA -ve IgM</th>
<th>Late RA -ve IgM</th>
<th>+ve IgG (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total</strong></td>
<td>40</td>
<td>24 (60)</td>
<td>11</td>
<td>13</td>
<td>16 (40)</td>
<td>5</td>
<td>12 (30)</td>
</tr>
<tr>
<td><strong>Males</strong></td>
<td>20</td>
<td>10 (50)</td>
<td>3 (27.2)</td>
<td>7 (53.8)</td>
<td>10 (50)</td>
<td>4 (80)</td>
<td>6 (54.5)</td>
</tr>
<tr>
<td><strong>Females</strong></td>
<td>20</td>
<td>14 (70)*</td>
<td>8 (72.7)*</td>
<td>6 (46.1)</td>
<td>6 (30)</td>
<td>1 (20)</td>
<td>5 (45.5)</td>
</tr>
<tr>
<td>Duration</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Early</strong></td>
<td>16</td>
<td>11 (68.7)*</td>
<td>0</td>
<td>0</td>
<td>5 (31.2)</td>
<td>0</td>
<td>4 (33.3)</td>
</tr>
<tr>
<td><strong>Late</strong></td>
<td>24</td>
<td>13 (54.1)</td>
<td>0</td>
<td>0</td>
<td>11 (45.8)</td>
<td>0</td>
<td>8 (66.6)</td>
</tr>
<tr>
<td>Joints affected</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>S+L</strong></td>
<td>22</td>
<td>16 (72.7)*</td>
<td>9 (80)</td>
<td>7 (53.8)</td>
<td>6 (27.2)</td>
<td>2 (40)</td>
<td>4 (36.3)</td>
</tr>
<tr>
<td><strong>S only</strong></td>
<td>18</td>
<td>8 (44.4)</td>
<td>2 (20)</td>
<td>6 (46.1)</td>
<td>10 (55.5)</td>
<td>3 (60)</td>
<td>7 (63.6)</td>
</tr>
<tr>
<td><strong>RF +ve</strong></td>
<td>20</td>
<td>10 (50)</td>
<td>4 (36.3)</td>
<td>6 (46.1)</td>
<td>10 (50)</td>
<td>4 (80)</td>
<td>6 (54.5)</td>
</tr>
<tr>
<td><strong>RF-ve</strong></td>
<td>20</td>
<td>14 (70)*</td>
<td>7 (63.6)</td>
<td>7 (53.8)</td>
<td>6 (30)</td>
<td>1 (20)</td>
<td>5 (45.5)</td>
</tr>
</tbody>
</table>

RA: Rheumatoid arthritis  
S: Small joints  
L: Large joints  
RF: Rheumatoid factor  
*p<0.05: Significant
Table 4: Incidence of B19 IgM in osteoarthritis patients and their clinical presentation.

<table>
<thead>
<tr>
<th></th>
<th>No.</th>
<th>+ve IgM</th>
<th>-ve IgM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>10</td>
<td>4 (40%)*</td>
<td>6 (60%)</td>
</tr>
<tr>
<td>Males</td>
<td>5</td>
<td>1 (20%)</td>
<td>4 (80%)</td>
</tr>
<tr>
<td>Females</td>
<td>5</td>
<td>3 (60%)*</td>
<td>2 (40%)</td>
</tr>
<tr>
<td>Polyarthritis</td>
<td>3</td>
<td>3 (100%)</td>
<td>0</td>
</tr>
<tr>
<td>Oligoarthritis</td>
<td>7</td>
<td>1 (14.3%)</td>
<td>6 (85.7%)</td>
</tr>
<tr>
<td>Joints affected S+L</td>
<td>9</td>
<td>3 (33.3%)*</td>
<td>(66.6%)</td>
</tr>
<tr>
<td>S only</td>
<td>1</td>
<td>1 (100%)</td>
<td>0</td>
</tr>
</tbody>
</table>

*p<0.05: Significant

Analysis of the clinical data of RA cases revealed that B19 IgM was more detected among females (70%) than males (50%) (p <0.05).

As regards the types of joints, there was 72.7% of cases had both large and small joints affected. This rate was statistically significant than the negative IgM cases (27.2%) (p <0.05) also this rate was higher than in positive patients who had only small joints affected (44.4%) (Table 3).

RA cases were complaining of pain and tenderness in their joints (87.5%). B19 IgM was detected in 60% of them. There was 9 cases complaining of manifestations of inflammation; redness, hotness and swelling, all of them were positive B19 IgM (Table1).

There were 11 early RA, (complaining of joint pain for less than one year). In these cases, 68.7%were B19 IgM positive. This rate was statistically higher than the IgM negative early RA cases (p<0.05). They were higher than the late RA cases (complaining for more than one year) (54.1%), but the difference was not statistically significant (p>0.05) (Table 3). Among the eleven early RA cases, B19 IgM was detected in72.7% female cases. This was statistically higher than that of the late RA cases (46.1%) (p<0.005) The majority of this group (80%) had large and small joint involvement, and they were statistically higher than those of the late RA cases (53.8%) (p <0.005) between the B19IgM negative cases, the reverse was recorded (Table 3).

RA cases were equally divided between seropositive and seronegative RF cases. B19 IgM antibodies were detected in 70% of RF seronegative cases, a statistically higher rate than those of IgM negative (30%) and higher than the RF seropositive cases (50%) (Table 3).
As regards RF, early RA patients with positive B19 IgM (63.6%) were seronegative RF. This was higher than that of the late cases with positive IgM (53.8%), but the difference was not statistically significant, the reverse was recorded in B19 IgM negative cases.

Among the studied group of RA, we found 23 cases of positive B19 IgG antibodies (57%), eleven of them were also positive to B19 IgM (27.5%). (Table 2).

In twelve RA cases, positive for B19 IgG, 83.3% were females, 66.6% late RA, 50% had large and small joint affected and 58.3% were RF seropositive.

Talking about the osteoarthritis-studied group, 4 cases were positive for B19 IgM (40%), 60% of them were females. Six patients of this group were positive for B19 IgG (60%); two of them had both B19 IgM and IgG.

Four patients of the SLE group were B19 IgG positive, and none was found B19 IgM positive.

DISCUSSION

The determination of antibodies response to B19 infection is considered an important tool in the diagnosis and in the identification of patients with either acute or chronic infection. Also, because the parvovirus is difficult to culture, parvovirus laboratory diagnosis is based primarily on serology (Nikkari et al., 1994).

In the present study, B19 IgM antibodies were detected in 60% of RA patients and 40% of osteoarthritis patients. These rates carried a highly statistically significant difference from both the negative control group and SLE group. In this aspect, Naides et al. (1993) reported that, especially in adults, arthropathies following primary infection with HPV B19 are common. B19 has attracted interest because of reports in adults of an arthropathy following infection that resembles RA and which may persist for a long time (Moore, 1998 and 2000).

RA patients positive to B19 IgM in the present study had a special clinical presentation. They were more among females (70%), duration of illness ranged from 3 months to one year (68.7%), with polyarthritis; large and small joints were more affected together with manifestations of acute inflammation, like joint pain and tenderness (60%), and limitation of movement (77.5%). RF was negative in 70% of them.

White et al. (1985) reported a similar presentation. They described B19-related arthropathy in young female adults who presented with an acute
symmetric arthritis involving peripheral joints. They added that, the musculoskeletal findings in the arthropathy syndrome usually resolve in two to four weeks, but persistence of symptoms may occur in patients for several years. In addition Kerr et al. (1996) described the same presentation among 80% of their B19 infected adults. This clinical presentation described in our study and in Kerr’s report was noticed in patients who were positive B19 IgM early RA cases (duration of illness 3 months to one year) more than the late RA cases (1 to 3 years of illness) or negative B19 IgM patients. This can confirm the causal association between B19 infection and acute arthritis.

Regarding the significance of RF in B19 arthropathy RF, Reid et al. (1985) reported that RF might be present or rise following B19 infection and parvovirus arthropathy is classically seropositive and non-erosive. To the contrary Kikkari et al. (1994) examined 47 cases of B19 arthropathy and RF was positive in only two of them.

Our results showed that, 70% of B19 IgM positive RA were RF negative; this rate was higher than RF positive cases and statistically higher than those were B19 IgM negative cases.

As regards the osteoarthritis cases of this work, B19 IgM was detected in 4 out of 10 patients (40%), a rate which is statistically significantly higher when compared to the control group. They were mostly females (60%), with polyarthritis (100%) of large and small joints (33.3%), their clinical presentation was similar to that of positive B19 IgM RA cases. This confirmed the suggestion of the implication of B19 in acute arthropathies, and not only in RA. This is supported by Saal et al. (1998) who detected B19 DNA in 16.7% of synovial biopsies taken from osteoarthritis patients. Kerr (2000) also supported this suggestion in his study about the pathogenesis of B19 in rheumatic diseases.

Talking about B19 in SLE in this study, B19 was not detected in SLE patients. These cases did not show any manifestation of acute inflammation. This observation can confirm the significance of B19 detection as a marker of acute B19 arthropathy (Kerr & Cunniffe, 2000).

Both B19 IgM and IgG were detected in 27.5% of RA cases and 20% of osteoarthritis patients in the present study during a long duration of illness. This goes against the theory of B19 as a trigger factor of RA. An explanation was suggested by Nacton et al. (1993) and confirmed by Nesher & Moore (1997), that the IgM is a prolonged response of an acute B19 infection, similar to the prolonged IgM response seen in some lyme arthritis patients. Another explanation is the possibility of subclinical infection after the beginning of arthritis symptoms (Moore et al., 1999).
B19 IgG was detected 30% in RA patients in the present study. Among them 83.3% were females whose clinical presentation was not typical as B19 IgM positive RA cases, but still differed completely from that of B19 negative RA patients. The same was recorded for osteoarthritis patients. As for SLE, there was no difference between positive and negative B19 cases. This observation does not exclude B19 IgG from being a diagnostic marker for B19 arthropathy, but detection of rising titer of these antibodies may be of great help (Nesher & Moore, 1997). Kalish et al. (1992) reported that differentiation between SLE and B19 infection was difficult, and that the possibility of B19 infection should be entertained in patients presenting with SLE-like features. The same finding was confirmed by Moore et al. (1999).

In the present study, B19 IgG was detected in 46.7% of the healthy control group; the difference between arthropathy cases and the controls was not statistically significant. This considerable rate of B19 IgG recorded in this study was also reported by Taylor et al. (1992). The presence of B19 IgG antibodies indicate previous infection but does not indicate its timing. Therefore, the results of the present work with the other mentioned Egyptian studies ring the bell for the considerable high prevalence of B19 circulation in the Egyptian community and the high risk of this virus as a causative agent of serious diseases specially in children (aplastic anemia) and pregnant women (hydrops fetalis), besides, its causal association with arthropathies.

Conclusion:

B19 should be added to the list of viral agents that cause joint manifestation. B19 arthropathy should be considered in the differential diagnosis in adults presenting with acute arthropathy. Early detection of B19 IgM or rising titers of B19 IgG antibodies may lead to early diagnosis of B19 arthropathies hence early treatment resulting less complication.
REFERENCES


فيروس البارفو في19 ودوره في التهاب المفاصل الحاد

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التاهيل***، كلية الطب جامعة عين شمس

الغرض من هذه الدراسة: هو معرفة نسبة وجود الأجسام المضادة للفيروس في19 و
القيمة الإكلينيكية لتعيينها في مرضى الرئيسي المفصلي ومرضى أم المفصل الحاد.

العنوان: تضم مجموعة البحث 40 مريضا بالرئيسي المفصلي وعشرة مرضى بالذئبة
الحماء و عشيرة أخرى مصابين بالعظام العظمي وأخرى مجموعة المقارنة وتضم عشرة من
الأصحاء من نفس الأعمار والأنواع.

الطريقة: وقد أجريت للجمع الاختبارات الليثية: قياس سرعة الترسب وقياس نسبة
الهيموجليوبين في الدم، قياس العامل الرئيسي بالدم بطريقة إمنكس ثم بطريقة الروزوالر، تحدد
وجود الأجسام المضادة للنواة بواسطة الميكروسكوب الفلوروسين، ثم تحدد وجود الأجسام
المضادة للفيروس في19 من نوعية البروتينات المناعية G و M بواسطة طريقة الإلزما. وقد
تمت مقارنة جميع التحالات بالحالة الإكلينيكية للمريض.

النتائج: وقد وجد أن الأجسام المضادة للفيروس في19 من النوعية
M وجدت في حالات الرئيسي المفصلي والعظام العظمي في حين لم يتم تعريفيها في حالات الذئبة الحماء.
على حين وجدت الأجسام المضادة من النوعية G في كل مجموعات المرضى و في الأصحاء
أيضا. و قد وجدت الأجسام المضادة من النوع M في الرئيسي المفصلي بنسبة 60% وذلك ذو
دارة إحصائية عالية مقارنة بباقي المجموعات وقد وجد أن معظم هذه المجموعات من النساء
(70%) وأغلبيهم من مرضى الرئيسي المفصلي سبب العلامة والمريض بالنسبة لون تراوح
بين 3 أشهر و سنة (مرض كمك) و المفاصل المتأثرة بالمرض تشتمل المفاصل الكبيرة والصغرى
على حد سواء أو بالنسبة لمجموعة الفصل العظمي. وجدت الأجسام المضادة في40% منهم معصم من النساء (60%)
والفاصل المصلي من المفاصل الكبيرة والصغرى معا
(75%) وقد وجد أن هذه الأرقام لها دارة إحصائية عالية لدى مقارنتها بمجموعة الأصحاء.

الاستنتاج: أن فيروس البارفو في19 يمكن اعتباره من الأسباب المؤدية للحالات لها
دارة إحصائية من حالات التهاب المفاصل الحادة وبالتالي يكون تحديد وجود الإصابة به من
العوامل المهمة في سرعة تحديد نوعية العلاج وذلك لتلقي المضاعفات التي تتنقل من تأخر
تحديد السبب و العلاج.