Benign Acute Childhood Myositis (BACM)으로 진단된 환아에서
임상양상, 혈액검사에 대한 고찰
동국대학교 임산병원 소아청소년과
정지윤・강은경・김도현・나소영・이정하・조성민

Clinical Features and Laboratory Findings in Children Diagnosed with Benign Acute Childhood Myositis (BACM)

Purpose: This study was performed to review the relationship between the clinical features and laboratory findings of patients suspected of benign acute childhood myositis (BACM) in children and adolescents with bilateral calf pain and gait disturbances.

Methods: From January 1, 2010 to December 31, 2016, the clinical and laboratory findings of patients who visited Dongguk University Ilsan Hospital with the sudden onset fever and muscle pain were retrospectively examined.

Results: The total number of patients was 29 (21 males and 8 females), and their mean age was 5.5 years. The mean duration of fever was 4.2 days. The mean duration from the onset of fever to show the symptom was 3.2 days. The mean recovery period from myositis was 2.4 days. The mean duration of hospitalization was 2.2 days. Fever and bilateral calf pain were the most common symptoms; however, cough, rhinorrhea, sore throat, headache, and abdominal pain were also observed. The causative agent of BACM was influenza B infection in 23 (79.3%) of the cases. Creatinine phosphokinase (CPK), myoglobin, aspartate aminotransferase (AST), and alanine transaminase (ALT) values were higher in the shorter duration of fever and were statistically significant. The following values were noted: CPK ($r=-0.472$), myoglobin ($r=-0.472$), AST ($r=-0.443$), and ALT ($r=-0.459$). The longer the pain period, the lower the white blood cell (WBC) count ($r=-0.655$).

Conclusion: BACM is mostly associated with the influenza B virus. Time to onset of symptoms after fever and WBC levels are related to muscle enzyme levels and duration of symptoms in BACM.

Key Words: Myositis, Influenza, Influenza B virus

Introduction

Benign acute childhood myositis (BACM) is a clinical syndrome manifested by the transient, sudden onset of calf pain and gait disturbance after a prodromal viral illness with elevated muscle enzymes.$^{1-3}$ BACM was first described by Lundburg as ’myalgia cruris epidemica’ in 1957.$^4$
BACM is mostly associated with the influenza B virus\(^2\)\(^-\)\(^9\). In particular, influenza-associated myositis has been reported to include rhabdomyolysis with symptoms of myalgia and systemic fatigue, but most often there is a good prognosis\(^1\)\(^-\)\(^3\)\(^-\)\(^10\).

Previous studies have reported the cause and clinical manifestations of BACM, but there has been a few study of the association between clinical features and laboratory test results. The purpose of this study was to investigate the retrospective data on the clinical features and laboratory findings of 29 patients diagnosed with BACM by showing leg pain and gait disturbance at the time of influenza epidemic, and to identify the factors related to the course of BACM.

Materials and methods

1. Patients

We retrospectively reviewed the medical records of 29 patients who visited Dongguk University Ilsan Hospital from January 1, 2010 to December 31, 2016.

In this study, BACM was defined as a self-limited clinical syndrome with clinical evidence of acute onset of fever, localized muscle pain, and CPK elevation. The exclusion criteria were presence of neurological deficit, immunologic disease.

2. Methods

Sex, age, family history, presence of underlying diseases, clinical symptoms, and treatment were recorded. In clinical symptoms, following variables were recorded: presence of fever, fever duration, pain site, pain duration, headache, abdominal pain and upper respiratory symptoms such as cough, rhinorrhea, sore throat.

Fever duration was converted into the time from the start of fever. The duration of symptoms was defined as the time from when the patient complained of symptoms until the day of symptom disappearance. Recovery was defined as complete absence of clinical symptoms.

Laboratory values were also recorded: complete blood cell count (CBC), C-reactive protein (CRP), CPK, creatinine kinase MB isoenzyme (CK-MB), myoglobin, AST, ALT, lactate dehydrogenase (LDH), creatinine and urinalysis.

3. Identification of causative agent

For the rapid influenza diagnostic test (RIDT), samples were obtained through nasopharyngeal swab. Influenza virus type A (H1N1, H3N2) and type B antigens were diagnosed by immunochromatography. For respiratory reverse transcriptase–polymerase chain reaction (RT-PCR), we used SEEPPER 12™ automated purification system which was loaded with the reagent, and the sample tube was then placed in the automated equipment (Seegene, Inc., Seoul, South Korea) and tested using a cDNA synthesis kit. Viruses were detected by means of data analysis using the CFX96™ Real-time PCR System (Bio-Rad laboratoryn Inc., USA).

Respiratory PCRs include 16 different viruses: influenza virus (A/B, total 2), respiratory syncytial virus (A/B, total 2), human rhinovirus, adenovirus, human metapneumovirus, parainfluenza virus (1/2/3/4, total 4), human coronavirus (229E/NL63/OC43, total 3), enterovirus, and human bocavirus. All 16 were qualitatively and quantitatively investigated.

4. Statistical analysis

All materials were analyzed using IBM SPSS Statistics ver. 20.0 (IBM, Inc., Armonk, NY, USA). The demographic, clinical characteristics and the laboratory results were analyzed using descriptive statistics, and the correlation between clinical symptoms and the laboratory findings were analyzed using nonparametric correlation analysis. The results are presented as means±standard deviation (SD) in the case of continuous variables. Discontinuous variables are described as frequency (%). The significance level of each statistical analysis was \(P<0.05\).

Results

1. Demographic characteristics

Of the 29 patients treated for BACM at Dongguk University Ilsan Hospital, 21 were male and 8 were female. The sex ratio was 72:28. The mean age was 5.5 years and ranged from 3 to 9 years. In this study, BACM mainly affected middle school-aged boys. The number of patients per year was 3 (10%) for 2010–2011, 11 (38%) for 2011–2012, 3 (10%) for 2013–2014, 3 (10%) for 2014–2015, and 9 (31%) for 2015–2016 (Fig. 1).

2. Clinical features

Of the 29 patients, the mean duration of fever was 4.2 days, and the period from the onset of fever to the onset of myositis was 3.2 days. The mean recovery time from the myositis symptoms was 2.4 days, and the average length of hospitalization was 2.2 days. A total of 19 out of 29 (65.5%) patients were hospitalized (Table 1).

Fever and calf muscle pain were the most frequently reported symptoms in the patients: however, cough, rhinorrhea, sore throat, headache, and abdominal pain were also reported.
Characteristically, muscle pain appeared in both lower limbs in all patients, and 26 of the 29 patients complained of pain in both calves. A total of four patients complained of pain in both thighs. A single patient complained of knee pain. Additionally, all study subjects showed a tendency to not walk or to walk abnormally due to pain (Table 1). Three (10%) cases showed muscle pain and gait disturbance without respiratory symptoms, such as cough, rhinorrhea, or sore throat. A total of four patients were referred to our hospital with Guillain-Barre Syndrome, and two of them showed deep tendon reflex (DTR) reduction.

### 3. Laboratory findings

On the first day of hospitalization, the mean serum CPK concentration was 2,350±2,554 IU/L (range 121–10,510 IU/L), the mean concentration of CK-MB was 55.9±85 IU/L (range 5–263 IU/L), and the mean concentration of myoglobin was 705±1,037 IU/L (range 88–3,988 IU/L). The mean values of serum AST and ALT were 100±77 IU/L (range 30–351 IU/L) and 28±14 IU/L (range 39–69 IU/L), respectively, and the mean value of LDH was 441±181 IU/L (range 207–1,001 IU/L).

The mean value of white blood cells was 4,140±1,400 μL (range 2,190–5,840 μL); for red blood cells, it was 12.9±0.8 g/dL (range 11.2–14.6 g/dL), and for platelets, it was 162±47 10³/μL (range 112–276 10³/μL). Of these, 15 (55.6%) patients had leukopenia, and 9 (31.0%) patients had thrombocytopenia. The mean value of CRP was 0.28±0.6 mg/dL (range 0.02–2.34 mg/dL), and for creatinine, it was 0.39±0.09 mg/dL (range 0.26–0.56 mg/dL) (Table 2).

The causative agents associated with BACM were influenza B (23 cases, 79.3%) and parainfluenza (1 case, 3%). No virus was detected in one (3%) of the children by the RIDT and the

---

### Table 1. Clinical Manifestations of Subjects

<table>
<thead>
<tr>
<th>Variables</th>
<th>Value (mean±SD, range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever duration (days)</td>
<td>4.2±1.7 (2–8)</td>
</tr>
<tr>
<td>Time (days)</td>
<td>3.2±1.3 (1–6)</td>
</tr>
<tr>
<td>Pain duration (days)</td>
<td>2.4±1.1 (0–4)</td>
</tr>
<tr>
<td>Hospital days (days)</td>
<td>2.2±1.9 (0–6)</td>
</tr>
<tr>
<td>Fever</td>
<td>29 (100)</td>
</tr>
<tr>
<td>Calf pain</td>
<td>29 (100)</td>
</tr>
<tr>
<td>Cough</td>
<td>19 (65.5)</td>
</tr>
<tr>
<td>Rhinorrhea</td>
<td>19 (65.5)</td>
</tr>
<tr>
<td>Sore throat</td>
<td>11 (37.9)</td>
</tr>
<tr>
<td>Headache</td>
<td>4 (13.8)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>3 (10.3)</td>
</tr>
</tbody>
</table>

### Table 2. Laboratory Findings on Admission

<table>
<thead>
<tr>
<th>Variables</th>
<th>Value (mean±SD, range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>White blood cell count, μL</td>
<td>4,140±140 (2,190–5,840)</td>
</tr>
<tr>
<td>Hemoglobin, g/dL</td>
<td>12.9±0.8 (11.2–14.6)</td>
</tr>
<tr>
<td>Platelet, 10³/μL</td>
<td>162±47 (112–276)</td>
</tr>
<tr>
<td>C-reactive protein, mg/dL</td>
<td>0.28±0.6 (0–2.34)</td>
</tr>
<tr>
<td>Creatine phosphokinase, IU/L</td>
<td>2,350±2,554 (121–10,510)</td>
</tr>
<tr>
<td>CK-MB, IU/L</td>
<td>55.9±85 (5–263)</td>
</tr>
<tr>
<td>Myoglobin, IU/L</td>
<td>705±1,037 (88–3,988)</td>
</tr>
<tr>
<td>Lactate dehydrogenase, IU/L</td>
<td>441±181 (207–1,001)</td>
</tr>
<tr>
<td>Aspartate aminotransferase, IU/L</td>
<td>100±77 (30–351)</td>
</tr>
<tr>
<td>Alanine transaminase, IU/L</td>
<td>28±14 (39–69)</td>
</tr>
<tr>
<td>Creatinine, mg/dL</td>
<td>0.39±0.09 (0.26–0.56)</td>
</tr>
</tbody>
</table>
respiratory virus PCR test. Four patients (13%) did not perform neither RIDT or respiratory PCR tests.

The period from the onset of fever to the onset of symptoms and CPK \( r=-0.472, P=0.011 \), myoglobin \( r=-0.472, P=0.023 \), AST \( r=-0.443, P=0.021 \), and ALT \( r=-0.459, P=0.016 \) showed significant negative correlations (Fig. 2). That is, the shorter the period from the onset of fever to the onset of symptoms, the higher the blood test values mentioned above.

There was a statistically significant negative correlation between WBC count and pain duration \( r=-0.655, P<0.001 \). There was no statistically significant correlation between WBC and fever duration.

LDH and CPK \( r=0.637, P=0.001 \) showed a statistically significant positive correlation. CK-MB \( r=0.761, P=0.028 \), myoglobin \( r=0.644, P=0.002 \), AST \( r=0.706, P(0.001) \), and ALT \( r=0.758, P<0.001 \) also showed positive correlations with LDH.

In this study, one patient showed positive results for myoglobinuria. A total of 21 out of the 29 patients were treated with oseltamivir. 18 patients had no abnormality in urine analysis, and one patient with myoglobinuria recovered without renal failure.

4. Relationship with the annual influenza epidemic

As known from previous literature and this study, influenza B is the most common cause of BACM, and we analyzed the relationship between BACM and the annual influenza epidemic with respect to the patients included in the study. The timing of the influenza epidemic was defined as the period of time when the incidence of influenza per 1,000 outpatients exceeds a certain number: this number is determined every year. According to the influenza epidemic announced by the Korean Disease Control Center (KCDC), groups were classified by year.

In the 2010–2011 group, one in three people developed influenza–associated BACM at the time of the influenza epidemic, and that patient tested negative on the RIDT. In the
2011–2012 group, 10 out of 11 patients developed influenza-associated BACM during the influenza epidemic, and, in all 10 cases, influenza B was detected by the RIDT or the PCR test. One patient did not test RIDT because this case did not occur during the epidemic. In the 2013–2014 group, 2 out of 3 patients developed the disease, influenza B was detected in two patients, and parainfluenza 1 was detected in the other. All three patients in 2014–2015 group and 9 patients in the 2015–2016 group developed BACM during influenza season, and influenza B was detected in all.

From the seasonal viewpoint of the association between influenza and BACM, 17 of 29 patients (59%) developed in May, and 5 (17%) developed in April. All of these were caused by influenza B, Two of the remaining 7 cases occurred during the influenza epidemic. One of the two cases was caused by parainfluenza virus, while the other one was caused by influenza A (Fig. 1).

Discussion

BACM is defined as a clinical syndrome characterized by transient muscle pain that occurs after a respiratory virus infection. The most common causative agent is influenza B9,10; however, influenza A11,12, enterovirus13, mycoplasma pneumoniae14, parainfluenza virus15,16, dengue virus17,18, and rotavirus19 have been reported as well.

The most prominent symptom of BACM is severe pain in the bilateral calves that develops suddenly; it results in characteristic gait disturbances, such as flat footsteps, stiff gait, trying not to support weight, or avoidance of walking20. In laboratory findings, BACM has been shown to be related to the prominent elevation of CPK21,22. In children, the prognosis is good and the symptoms usually improve within a week11,12. Nephrotic syndrome and rhabdomyolysis are rare serious complications; they are also rare in adults20.

Previous reports have shown that the sudden onset of bilateral calf pain and difficulty in walking after an acute respiratory tract illness6–9,11,21,22,13. CPK elevation is believed to have occurred as a result of muscular damage to the affected area, such as the calf. Based on these results, CPK, CK-MB, and myoglobin could be further examined in patients with fever, muscle pain, and gait disturbances. In most hospitals, LDH is included in the routine laboratory test. In case of myositis, CK, CK-MB and myoglobin were thought to be caused by viral infections including influenza21,22. The duration of fever was considered as a disturbance variable, but there was no statistically significant relationship between it and WBC (P=0.456).

LDH showed a positive correlation with CPK, CK-MB, myoglobin, AST, and ALT. LDH is known to be a useful index for the evaluation of hemolysis, as well as muscle and tissue damage, and it was elevated in all patients in this study. Although the etiology and mechanism of BACM are unclear, they are thought to be associated with the inflammation and injury of muscle cells, including pathologically degenerative changes of muscle cells and local muscle fiber vacuoles and muscle necrosis11,12,23. CPK elevation is believed to have occurred as a result of muscular damage to the affected area, such as the calf. Based on these results, CPK, CK-MB, and myoglobin could be further examined in patients with fever, muscle pain, and gait disturbances. In most hospitals, LDH is included in the routine laboratory test. In case of myositis, CK, CK-MB and myoglobin

Table 3. Antigenicity of Influenza Isolated by Hemagglutination-Inhibition Test and Vaccination in Korea

<table>
<thead>
<tr>
<th>Years</th>
<th>Influenza antigenicity</th>
<th>Vaccine</th>
<th>Number of patients (N=29)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010–2011</td>
<td>B/Brisbane/60/2008 (Victoria), B/Florida/4/2006 (Yamagata) (22)</td>
<td>B/Brisbane/60/2008 (22)</td>
<td>3</td>
</tr>
<tr>
<td>2011–2012</td>
<td>B/Brisbane/60/2008 (Victoria, 73%), B/Florida/4/2006 (Yamagata, 27%) (23)</td>
<td>B/Brisbane/60/2008 (23)</td>
<td>11</td>
</tr>
<tr>
<td>2012–2013</td>
<td>B/Wisconsin/1/2010 (Yamagata), B/Brisbane/60/2008 (Victoria) (24)</td>
<td>B/Wisconsin/1/2010 (24)</td>
<td>0</td>
</tr>
<tr>
<td>2013–2014</td>
<td>B/Massachusetts/2/2012 (Yamagata), B/Brisbane/60/2008 (Victoria) (25)</td>
<td>B/Massachusetts/2/2012 (25)</td>
<td>3</td>
</tr>
<tr>
<td>2014–2015</td>
<td>B/Massachusetts/02/2012-like (26)</td>
<td>B/Massachusetts/02/2012-like (26)</td>
<td>3</td>
</tr>
<tr>
<td>2015–2016</td>
<td>B/Texas/2/2013 (Victoria), B/Phuket/3073/2013 (27)</td>
<td>B/Phuket/3073/2013 (27)</td>
<td>9</td>
</tr>
</tbody>
</table>
should be additionally prescribed, so if the LDH is increased through this association, prescribing the remaining test may help reduce the costs.

In this study, 21 of the 29 patients were treated with antiviral therapy using oseltamivir. These were patients who had been diagnosed with influenza within 48 hours of the onset of fever. All of the patients in this study showed symptomatic improvement with appropriate supportive therapy, and no serious complications were seen. There have been reports of complications such as rhabdomyolysis, acute renal failure, and myocarditis in international studies and case reports. In this study, use analysis was done in 21 of 29 patients, and 4 cases showed abnormal findings. Blood 3+ and microscopic red blood cell (RBC) 10–29/HPF were detected in one patient's urine test which was normalized in three days. Urine ketones were detected in two other patients.

The myoglobinuria was reported in one patient. In this patient, serum myoglobin was found to be 3,987.8 IU/L, and a urine myoglobin test confirmed this. The urinalysis showed protein 1+, blood 3+, microscopic RBC 1–4/HPF, and urine myoglobin 1,740 IU/L. This patient recovered with the use of fluid therapy, antipyretics, and antiviral medication. Thus, screening for urine myoglobin in patients with high serum myoglobin levels may be helpful.

A total of four cases referred from the primary hospital because of Guillain–Barre Syndrome were suspected due to decreased DTR on the physical examinations. Consequently, all cases were diagnosed as BACM. Respiratory PCR was performed in four patients, and three patients were identified with influenza B and one patient with parainfluenza 1. It is necessary to differentiate Guillain–Barre Syndrome from BACM and other musculoskeletal diseases by physical examinations, such as DTR and laboratory findings in patients exhibiting fever, respiratory symptoms, calf muscle pain, gait disturbances and elevated muscle enzymes in blood tests.

Cases of recurrent BACM have also been reported. One recurrent BACM case experienced occurrences of fever, myalgia, and gait disturbances in 2010 and 2013. In this patient, CPK was also elevated in all 2 events, but was completely reversed without complications.

Influenza B virus is the most common causative agent in virus–associated myositis. Influenza B virus is a national notifiable infectious disease in Korea, and there is it domestic influenza surveillance system at the KCDC and prevention which is used to collect data on it. Using this data, the influenza antigenicity and vaccine strain were analyzed by means of a hemagglutination-inhibition test (HI) with standard antigens and anti-serum provided by the World Health Organization (WHO). The data are shown in Table 3. The ratio of B/Florida/4/2006 in the Yamagata strain that was not included in the vaccine tended to increase in the 2011–2012 group, when the number of patients was highest in the present study. In the 2015–2016 group, the B/Texas/2/2013 of the vaccine in the Victoria strain showed a tendency to prevail. Presumably, if the influenza type of the antigen not included in the vaccine is prevalent, it can be considered that the incidence of the BACM is high.

There are considerable reports of clinical manifestations of BACM and the elevation of CPK. In Korea, a case of influenza B associated myositis and clinical symptoms of children complaining of myositis due to influenza B infection were reported. Jung et al. reported 16 influenza B associated BACMs, and in Lim et al., seven patients were reported, of whom two had influenza B. In Lim's study, the mean age of onset was high, and all were school-aged children. The results of hematologic tests including the muscle enzyme showed no significant difference. In Jung's study, the time to recovery from myositis was similar to our study, but the duration of hospitalization was shorter in our study. Although antiviral treatment presumed to have influenced the duration of hospitalization, further studies are needed. The advantage of our study is that we have further explored the relationship between blood tests and clinical features in BACM. The advantage of our study is that we can estimate the relationship between the clinical features and the blood test, and we can predict the duration of symptoms according to the blood test results. The other things we learned from our study are that BACM not only occurs during influenza epidemics, so should also be considered when there are other viral diseases and the possibility of recurrence.

The limitation of this study is that we don’t know about the influenza B antigenicity and the vaccination strain of the enrolled children. There have been no studies on the relationship between viral antigenicity and BACM. Therefore, to determine the relationship between the antigenicity of influenza and BACM, further studies are needed.

요약

목적: 양측 하지의 통증과 보행장애로 소아청소년과에 내원하여 BACM으로 의심되거나 진단된 환자들의 임상양상과 혈액검사 간의 연관성을 살펴 보기 위해서 본 연구를 시행하였다.

방법: 2010년 1월 1일부터 2016년 12월 31일까지 동국대학교 일산
병원에 내원한 환아 중 갑작스런 발열과 더불어 근육통의 임상적 증가가 있으면서 근효소 검사를 시행한 환자를 대상으로 임상양상, 혈액검사 소견을 후향적으로 조사하였다.

결과: 총 환자는 29명(남 21명, 여 8명)이고 평균 연령은 5.5세였다. 발열기간은 평균 4.2일, 발열이 시작된 후 근염 발현까지의 기간은 평균 3.2일이었다. 근염 증상의 평균 회복기간은 2.4일, 평균 재원기간은 2.2일이었다. 발열, 양측 종아리 근육통이 가장 흔한 증상이었으며, 그 외에 기침, 콧물, 인후통, 두통, 복통이 나타났다. BACM의 원인 병원체로는 influenza B 감염이 23명(79.3%)으로 가장 많았다. 발열이 시작된 후 증상이 나타나기까지 시간이 짧을수록 CK, myoglobin, AST, ALT 값이 높게 나타났으며, 통계적으로 유의하였다. \[CPK \ (r = -0.472), myoglobin \ (r = -0.472), AST \ (r = -0.443, ALT \ (r = -0.459)\] 통증 기간이 길수록 WBC가 낮게 나타났다. \[r = -0.655\]

결론: Influenza B 감염이 BACM의 가장 흔한 원인이다. 발열부터 증상 발현까지의 시간과 WBC 수치는 BACM에서 근육 관련 효소 수치와 증상 지속 시간과 관계가 있다.

References