양성 소아기 근염과 연관된 B형독감 유행

해운대백병원 소아청소년과

허윤정

Outbreak of Influenza B related to Benign Acute Childhood Myositis

Yun Jung Hur, MD, PhD

Department of Pediatrics, Haeundae Paik Hospital, Inje University College of Medicine, Busan, Korea

Purpose: Benign acute childhood myositis (BACM) is a rare syndrome caused by a viral infection and is characterized by gait disturbance with calf pain in children. I investigated whether BACM is related to the incidences of seasonal influenza and of specific influenza subtypes in Korea.

Methods: Patients diagnosed with BACM between March, 2010 and December, 2014 were investigated retrospectively. The occurrence of BACM was compared with the incidence of influenza for each influenza season, as obtained from the Korea Centers for Disease Control and Prevention.

Results: All patients had previous infection preceding calf muscle pain or gait disturbance. Laboratory findings showed elevated levels of creatine kinase (median, 1243 U/L) and leukopenia ($<4500/\mu\text{L}$). Patients exhibited benign courses that resolved within a few days without any complications. The rate of influenza B was correlated with BACM occurrence ($P=0.05$) although this relationship was not statistically significant. Neither the rate of total influenza nor the rate of influenza subtype A was associated with BACM occurrence.

Conclusion: The outbreak of influenza B was correlated with the occurrence of BACM. We should recognize the occurrence of this disease and avoid unnecessary evaluation to diagnose BACM when an outbreak of influenza B is expected.

Key Words: Creatine Kinase, Influenza B virus, Myositis

Introduction

The incidence of influenza virus differs across seasons, areas, age groups and viral subtypes. The manifestations of infection with this virus range from common symptoms, such as cough, rhinorrhea and fever, to rare symptoms such as seizure¹⁾. Common influenza-related complications include otitis media, particularly in younger children. Influenza can also cause pneumonia, which often requires hospitalization. Neurologic complications can also result from influenza virus infection; Asian children are particularly vulnerable to such complications^{1,2)}. These complications range from mild to severe and can be fatal. The most common mild form is febrile convulsion³⁾. Other manifestations include encephalitis, encephalopathy, seizure, Guillain-Barre syndrome, transverse myelitis and infectious myositis. Infectious myositis is rarely caused by influenza, but it sometimes appears in combination with severe neurologic manifestations

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Correspondence to Yun Jung Hur, MD, PhD
Department of Pediatrics, Haeundae Paik Hospital,
875, Haeundaero, Haeundaegu, Busan 48108, Korea
Tel: +82-51-797-2006, Fax: +82-51-797-2713
E-mail: H00105@paik.ac.kr

such as rhabdomyolysis³⁾. Patients with infectious myositis usually complain of sudden-onset ataxia, painful leg cramps or an inability to walk⁴⁾. Gait ataxia must be differentiated from peripheral neuropathy and central nervous system (CNS) disease.

Infectious myositis typically exhibits an acute and benign course in children, while the benign course does not occur in adults or the elderly. Benign acute childhood myositis (BACM) has a low incidence but may be associated with viral infection including influenza virus^{4,5)}. However, due to its rarity, BACM is often not recognized and further evaluations to differentiate BACM from central or peripheral nervous system disease may be performed. Thus, I studied the clinical and laboratory manifestations of childhood patients with acute infectious myositis. I also analyzed the relationships between BACM and the occurrence of seasonal influenza and of specific influenza subtypes in Korea. Better knowledge regarding these relationships will enable us to recognize and differentially diagnose BACM without unnecessary evaluation.

Materials and Methods

Patients diagnosed with BACM between March 2010 and December 2014 were investigated retrospectively. Patients who were younger than 18 years of age were included. Data regarding the clinical characteristics and laboratory findings of patients with BACM were collected. Diagnostic criteria for BACM included the abrupt onset of calf muscle pain or gait disturbance after respiratory tract infection (up to 14 days), accompanied by an elevation of creatine kinase (CK, normal range: 50–200 U/L). Patients with underlying neuromuscular disease were excluded. To identify the causes of respiratory tract infections, nasopharyngeal swabs were assessed via real-time polymerase chain reaction (Advasure Kit; LG Life Sciences, Korea) for respiratory viruses, including rhinovirus, adenovirus, respiratory syncytial virus, parainfluenza, metapneumovirus, influenza A, influenza B, bocavirus, and coronavirus. A chemiluminescence immunoassay (LIASION, DiaSorin S.P.A., Italy) was used to assess blood samples for mycoplasma pneumonia. In cases of suspected dengue virus infection, the Korea Centers for Disease Control and Prevention was asked to perform the appropriate blood tests, which involved immunochromatography assays. Our study was approved by the institutional review board of Inje University Haeundae Paik Hospital, and the data were analyzed without information regarding patient identities.

The occurrence of influenza for the influenza seasons from September to the following May between 2009 and 2014 was investigated, as the epidemic period of influenza typically extends from fall to spring. The occurrence and statistical data

for influenza for each influenza season in Korea were obtained from the Korea Centers for Disease Control and Prevention (www.cdc.go.kr), which confirms on a weekly basis the monitoring by 200 hospitals nationwide of infections of influenza and respiratory virus, including adenovirus, parainfluenza, respiratory syncytial virus, enterovirus, bocavirus, coronavirus, rhinovirus and metapneumovirus. To evaluate the relationship between influenza outbreaks and the occurrence of BACM, the occurrence of influenza from September to the following May for each influenza season, as reported by the Korea Centers for Disease Control and Prevention, was compared with the occurrence of BACM during that season. Data regarding the occurrence of influenza at our hospital were collected using the same approach for all influenza seasons except for 2009–2010, during which data were collected from March 2010 to May 2010 because our hospital opened in March 2010.

The relationships between the occurrence of influenza infection and BACM were statistically evaluated using Spearman's correlation analysis and Fisher's exact test; these assessments were conducted using SPSS Statistics for Windows, version 23.0 (IBM Corp., Armonk, New York). $P < 0.05$ was considered to indicate statistical significance.

Results

Fifteen patients were diagnosed with 17 episodes of BACM, which is characterized by acute-onset calf pain and infectious myositis with elevated CK. The clinical characteristics and laboratory findings are described in Table 1. All patients had a

Table 1. Clinical Characteristic of Patients with Benign Acute Childhood Myositis

	Cases (N=17)	Median (range)
Age (years)		6.6 (2.0-11.0)
Sex (M:F)	15	12:3
Presence of fever	17	
Interval between onset of calf muscle pain and respiratory symptoms (days)		3.0 (2-6)
Duration until resolution of calf muscle pain (days)		3.0 (2-6)
Initial leukocytes (/ μ l)		3,750 (2,210-5,260)
Lymphocytes (%)	16	54.3 (28.6-81.3)
Initial CPK (U/l)		1,243 (279-10,000)
Aspartate aminotransferase (U/l)		72 (32-446)
Alanine aminotransferase (U/l)		5 (41.7)
Creatinine (mg/dl)	16	0.5 (0.42-0.7)
Serum-myoglobin (ng/ml)	5	183 (55-4040)
Urine myoglobin with a positive finding (N)	10	1
Lactate dehydrogenase (U/L)	15	313 (220-694)
Influenza-positive (A:B)	11 (64.7%)	2:9

CK, creatine kinase.

fever ($\geq 38^{\circ}\text{C}$) with respiratory symptoms that preceded calf muscle pain or gait disturbance (by up to 7 days) and exhibited elevated CK levels (median, 1,243 U/L). None showed excessive exercise in history taking. They showed normal deep tendon reflexes, and neurologic examinations produced normal findings. The results of cerebellar function tests and cranial nerve function tests were normal. The laboratory findings including electrolytes except for Table 1 were normal and the physical examinations were normal in all patients. All patients exhibited benign courses that resolved within a few days without any complications such as acute renal failure. BACM occurred predominantly in the winter and spring, corresponding to the epidemic period of influenza, except for one case involving a patient diagnosed with parainfluenza virus in August. Leukopenia ($<4,500/\mu\text{L}$) and lymphocytosis ($>50\%$) were observed in eleven and ten cases, respectively. Hip and leg X-rays were obtained in eight cases, including one case involving sonography for both hips and one case involving a cerebral spinal fluid examination that produced normal findings. No patients underwent magnetic resonance imaging or computed tomography of the brain, hips or legs. The causes of infections that resulted in BACM were influenza virus in 11 cases (subtypes A and B in 2 and 9 cases, respectively), parainfluenza virus in two cases, and dengue virus in one case; viruses were not detected in two cases. One patient did not undergo testing for viral identification. A boy of seven years and seven months with BACM caused by dengue virus presented with CK levels as high as 10,000 U/L, positive findings for urine myoglobin and serum creatinine levels in the normal range. He travelled around the Philippines and had been bitten by mosquitoes. He received hydration with normal saline, and his condition resolved without any complications such as cardiac muscle involvement within four days. Two patients with BACM caused by influenza and by

another virus experienced recurrence two years later. One patient experienced BACM caused by influenza B and then presented with BACM caused by an unknown agent two years later; the other patient first presented with BACM caused by parainfluenza virus and then exhibited BACM caused by influenza B two years later. Common factors for recurrence were not detected for these two patients.

To evaluate the relationship between the outbreak of influenza in Korea and the occurrence of BACM, the incidence of influenza was compared with the occurrence of BACM for each year (Table 2). Neither the positivity rate for influenza for all samples nor the positivity rate for influenza subtype A was correlated with BACM occurrence. However, among influenza-positive patients, the rate of influenza B was correlated with BACM occurrence (coefficient 0.87, $P=0.05$), although this relationship was not statistically significant. To assess the relationship between the outbreak of influenza in our hospital and the occurrence of BACM, the incidence of influenza was compared with the occurrence of BACM for each year (Table 2). The detection rate of influenza B among influenza-positive patients in our hospital was correlated with the occurrence of BACM (coefficient 0.87, $P=0.05$). No influenza data from September 2009 to February 2010 were obtained in our hospital, and the rate of influenza B among influenza-positive patients in our hospital was correlated with BACM occurrence (coefficient 0.95, $P=0.05$) when we reanalyzed the remaining data. The occurrence of BACM was significant during the 2009–2010, 2011–2012 and 2013–2014 influenza seasons, with an outbreak of influenza subtype B occurring once every two years (Fisher's exact test, $P<0.05$).

Table 2. Relationships between Influenza and Benign Acute Childhood Myositis Occurrence

	2009-2010	2010-2011	2011-2012	2012-2013	2013-2014
All samples in KCDC	14118	8660	11594	10116	9442
Influenza (N, %)	6,345 (44.9)	1,960 (22.6)	3,755 (32.4)	1,659 (16.4)	2,080 (22.0)
Influenza A (N, %)	4,733 (66.2)	1,946 (99.3)	1,941 (51.7)	1,593 (96.0)	982 (47.2)
Influenza B (N, %)*	1,612 (33.8)	14 (0.7)	1,814 (48.3)	66 (4.0)	1,098 (52.8)
Influenza B among all samples (%)	11.4	0.16	15.6	0.65	11.6
All samples in our hospital	305	953	1413	721	985
Influenza (N, %)	43 (14.1)	129 (13.5)	433 (30.6)	81 (11.2)	239 (24.2)
Influenza A (N, %)	2 (4.7)	128 (99.2)	228 (52.7)	79 (97.5)	109 (45.6)
Influenza B (N, %)	41 (95.3)	1 (0.8)	205 (47.3)	2 (2.5)	130 (54.4)
Influenza B among all samples (%)	13.4	0.1	14.5	0.3	13.2
BACM caused by influenza (N=11)*	3	1	3	0	4

KCDC, Korea Centers for Disease Control and Prevention; BACM, benign acute childhood myositis.

*Spearman's correlation analysis ($P=0.05$).

Discussion

BACM is a rare syndrome caused by viral infection and is characterized by gait disturbance with calf pain in five- to eight-year-old children; furthermore, it exhibits male predominance. In cases involving acute gait disturbance, cerebral spinal fluid analysis, ultrasonography, magnetic resonance imaging, and nerve conduction velocity evaluation can be performed to differentiate BACM from other diseases, including arthritis, Guillain-Barre syndrome, and transverse myelitis, among others^(6,7). Eight patients underwent hip and leg X-rays and ultrasonography to differentiate BACM from arthritis and other forms of myositis because their emergency department physician was not familiar with BACM^(5,8). One patient who complained only of gait disturbance initially underwent cerebral spinal fluid analysis, as a normal deep tendon reflex can be observed during the early period of Guillain-Barre syndrome⁽⁹⁾ and the histories are similar between BACM and Guillain-Barre syndrome, both of which are preceded by acute febrile illness. Typically, patients with BACM complain of calf muscle pain after acute febrile illness, with CK elevation manifesting a few days later. BACM is often resolved within a few days without any complications, although recurrent myositis can develop^(10,11). All but one experienced calf muscle pain after febrile illness, with a median time interval between these manifestations of 3 days in this study. They presented with CPK elevation without abnormal creatinine and leukopenia, as shown in a previous study⁽⁴⁾. Knowledge of the typical history, laboratory findings and normal neurologic examination results associated with BACM can help prevent unnecessary evaluation^(5,8). However, other neurologic diseases, including rhabdomyolysis, Guillain-Barre syndrome, inflammatory myositis, and transverse myelitis, must be excluded when atypical or obscure signs or symptoms are present⁽¹²⁾.

In Korea, influenza is prevalent every year, irrespective of subtype, and influenza B outbreaks occur every two years. Influenza infection presents with various complications, such as pneumonia and otitis media in children, but it seldom causes neurologic complications. One investigation indicated that influenza A (H1N1) pdm09 caused neurologic involvement in 1.7% of infected patients, of whom 67% had seizures; most patients with neurologic involvement showed mild neurologic symptoms, with a good prognosis observed for Korean children⁽²⁾. Several studies have reported that BACM is associated with influenza infection, particularly infection with influenza subtype B^(13,14). In a prior investigation, most patients with influenza infections were affected by fever, which was particularly common among children (with a median age of 6.2 years)⁽¹⁾. Another previous study reported that CPK elevation was associated more strongly with influenza infection in

children than in adults⁽¹⁵⁾. In BACM, muscle biopsies showed necrosis with active degeneration and focal vacuolation suggesting to monophasic myositis⁽⁴⁾. Direct viral invasion with failure to replicate in the muscle may occur in BACM, and influenza B has been detected in infected muscle⁽¹²⁾. In the present study, the outbreak of influenza B was correlated with the occurrence of BACM. The rate of influenza B positivity among all influenza cases can be informative regarding the occurrence of BACM. The incidence of BACM appeared to increase in association with influenza B but was not related to either influenza A or the overall outbreak of influenza. In our hospital, the incidence of BACM was specifically correlated with the occurrence of influenza B infection, based on comparisons of each influenza season and their trends from 2009/2010 to 2013/2014. Therefore, the occurrence of BACM should be considered when an outbreak of influenza B virus is expected.

The limitations of our study include its small sample size, which occurred because BACM is a rare disease, and the use of data from only a single center. Given the small number of BACM occurrences in our study, the statistical power was weak. Although more reliable data are obtained in single-center studies than in multicenter investigations, single-center studies generally have small sample sizes, leading to weak statistical analyses. To obtain additional information regarding the association between influenza B and BACM, a multicenter study will be necessary.

요약

목적: 소아기 근염은 바이러스 감염에 의해 발생하는 드문 질환으로 종아리 근육의 통증과 보행장애를 특징으로 한다. 그래서 양성 소아기 근염에서 독감바이러스와의 관계, 특히 그 아형에 따른 원인을 확인하고자 하였다.

방법: 2010년 3월부터 2014년 12월까지 해운대 백병원에서 양성 소아기 근염을 진단받은 환자를 대상으로 후향적으로 조사하였다. 우리는 양성 소아기 근염의 발생률을 각 분기별에 대한 질병관리본부에 보고된 독감바이러스 발생뿐만 아니라 해운대 백병원에서 진단된 독감바이러스 환자의 발생률을 각각 비교하였다.

결과: 양성 소아기 근염으로 진단된 환자들의 검사에서 creatine phosphokinase (median, 1,243 U/L) 증가와 leukopenia ($<4,500/\mu\text{L}$) 소견을 확인할 수 있었다. 환자들은 모두 3-5일 이내에 증상이 호전되는 양성경과를 보였으며 이에 따른 합병증은 보이지 않았다. 독감바이러스의 발생률과 그 아형인 A형 독감의 발생률과 양성소아기 근염의 발생률은 연관성을 찾기는 힘들었으나 B형 독감의 발생률과는 연관성이 있었다(coefficient 0.872, $P=0.05$).

결론: 양성 소아기 근염은 독감바이러스 중 B형 독감과 연관성이 있을 수 있다 그러므로 독감 바이러스 중 독감 B형의 유행시 이 질환

에 대한 경각심을 알고 종아리 통증을 동반한 보행장애를 주소로 내원한 환자 발생시 불필요한 진단 및 치료를 피하는 것이 좋겠다. 다만 논문의 샘플수가 작아서 추가적인 다기관 연구가 필요할 것으로 보이며 B형 독감이 유행하는 시기라고 하더라도 다른 질환과의 감별을 염두 해야 한다.

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