Influenza-Associated Myositis in Children
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Abstract
Background: Influenza-associated myositis (IAM) is an infrequent and poorly known complication of influenza virus infection in children. The aim of this study was to describe five cases of IAM and to review the literature on IAM in children.

Patients and Methods: We conducted a retrospective analysis of cases of IAM diagnosed at two university children’s hospitals in Switzerland during two consecutive influenza seasons. Findings were compared with 39 individual case reports and five publications summarizing an additional 272 cases identified by a medical online library (MEDLINE) search.

Results: Overall, 316 cases were analyzed. IAM typically occurred in school-aged children with a 2:1 male predominance. Influenza B and A viruses were identified in 76% and 24% of cases, respectively. The median interval between onset of influenza and onset of IAM was 3 days (range 0–18). The calf muscles were involved alone or together with other muscle groups in 69% and 31% of cases, respectively. Blood creatine phosphokinase (CPK) concentration was invariably elevated. Median duration to clinical recovery was 3 days (range 1–30). Rhabdomyolysis occurred in ten of 316 patients (3%), more often associated with influenza A (86%), and led to renal failure in eight patients (80%).

Conclusion: Clinical and laboratory findings of IAM are highly characteristic and allow a rapid diagnosis during the influenza season.

Introduction
Influenza is a common and usually benign viral respiratory tract infection occurring worldwide in annual epidemics during the cold season. According to established medical knowledge, complications are mainly seen in the elderly. Recent studies, however, indicate that influenza-associated morbidity in children may be greater than previously thought [1, 2]. Complications mainly affect the respiratory tract and the central nervous system. Another complication of influenza, which has only sporadically been reported since its first description in 1957 [3], is influenza-associated myositis (IAM). IAM appears to be more common in children than in adults, but its age-specific incidence during influenza epidemics is unknown. As IAM has typically been associated with the influenza B virus, its incidence may depend on the nature of circulating strains during a given epidemic.

There is no standardized nomenclature of IAM in the literature and the pathogenetic events leading to muscle involvement have not been elucidated in detail. Nevertheless, both the clinical presentation and laboratory characteristics of IAM seem fairly typical. Clinical manifestations can be dramatic and IAM often causes diagnostic confusion because it is a poorly known entity in the medical community. Although IAM usually follows a benign and self-limiting course, several cases with a severe course and life-threatening complications have been reported.

The aim of this study was to review recent experiences with IAM at two large pediatric hospitals in Switzerland and to review the medical literature.

Patients and Methods
Definitions
IAM was defined as follows: Virologically proven influenza or influenza-like illness plus clinical evidence for localized myalgia plus elevation of serum creatine phosphokinase (CPK) or abnormal muscle biopsy in a patient younger than 16 years of age. The term “rhabdomyolysis” was reserved arbitrarily for patients who also had myoglobinuria.

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Patients
Medical records from children with IAM, who were seen at the University Children’s Hospitals of Bern or Basel, Switzerland, during the influenza seasons in 2002 and 2003, were analyzed. The following set of clinical data was retrieved for each patient: age, gender, reason for referral, duration and characteristics of influenza or influenza-like illness, muscle symptoms, other symptoms and signs, laboratory parameters at presentation (i.e., peripheral white blood cell count, serum C-reactive protein, CPK, aspartate transaminase (ASAT), alanine transaminase (ALAT), creatinine, and urinalysis), duration and course of illness, and outcome.

Laboratory Detection of Influenza Virus
Nasopharyngeal secretions (NPS) were sampled using a VYGON infant mucus aspirator (Ecouen, France) and assessed for the presence of influenza A and B using a direct immunofluorescence assay (Light Diagnostics Respiratory Panel DFA, Chemicon International, Inc., Temecula, CA, USA) or by a multiplex polymerase chain reaction (PCR). This method was designed to amplify cDNA specific for influenza A and B, respiratory syncytial virus (RSV), parainfluenza virus types 1 and 3, and adenovirus. Viral RNA was purified from NPS by use of the QIAamp Viral RNA kit (Qiagen, Basel, Switzerland), and cDNA was synthesized by means of reverse transcriptase PCR (Titan One Tube RT-PCR System, Roche, Basel, Switzerland). Multiplex PCR was performed in two separate assays. One assay contained specific primers for influenza A, influenza B, and parainfluenza virus type 1. Amplification products were sequenced.

Results
Our Cases
We identified five patients with IAM (Table 1). Private pediatricians referred four patients, one patient with severe calf pain presented to the emergency room. In four patients, the reason for referral was incapacitating calf pain. Suspected diagnoses were Guillain-Barré syndrome in three patients, deep venous thrombosis in one, and cerebellar ataxia in one. The median age was 8.3 years (range 7.3–10.3). All patients had a history of a recent influenza-like illness starting 2 to 5 days before presentation and consisting of fever and rhinorrhea. Additional complaints were sore throat, nausea, cough, and headache in patient 1, cough in patient 2, and headache and dizziness in patient 4. In patients referred by their private physician, muscle symptoms had started 1 to 2 days before presentation. Patient 3 presented on the day myalgia had started. The median interval between the onset of influenza and the onset of muscle symptoms was 2.5 days (range 0–4).

During clinical examination, all patients were afebrile, had normal vital signs, and appeared non-toxic. No influenza-associated respiratory signs were present in patients 3 and 4. Rhinorrhea was observed in patients 1, 2, and 5. Pharyngitis was observed in patient 1. The predominant clinical manifestation in all patients was severe pain and localized tenderness of the calf muscles bilaterally, which led to abnormal gait or refusal to walk. Neurologic examination was normal. There was no gross hematuria. IAM was suspected in all patients and confirmation was achieved by demonstrating massively elevated serum CPK concentrations. Myoglobinuria was found in patient 4. Influenza virus infection was documented in four patients by demonstration of influenza A or B virus in NPS. Two patients were hospitalized briefly. All patients had a favorable outcome. No complications or sequelae were recorded.

Review of the Literature
We identified 311 cases of IAM [3–36]. Ten patients had recurrent episodes [3, 4, 17, 18, 34]. Of 294 patients in whom the gender was noted, 200 were male, resulting in a gender ratio of 2:1. Detailed data were available from the reference group consisting of 39 patients (Table 2). The median age was 8.5 years (range 2.5–14). Lundberg [3] reported a median age of 9 years, Mackay et al. [34] and Farrell et al. [17] found a mean age of 8.1 and 7 years, respectively. In the reference group, the median interval between the onset of influenza-associated symptoms and the onset of muscle symptoms was 3 days (range 0–18). Lundberg [3], Mackay et al. [34] and Farrell et al. [17] found a median interval of 2.6, 5 and 5 days, respectively. In the reference group the most frequent influenza-associated symptom was fever (74%), followed by cough (33%), rhinorrhea (26%), nausea and vomiting (23% each). Lundberg [3] recorded fever in 92%, headache in 80%, and rhinitis and cough in 49% and 46%, respectively. Nausea and vomiting were present in 41%. In the reference group, muscle pain was located exclusively in the lower extremities in 69%, particularly in the calf muscles. Involvement of the upper extremities occurred in 20% of cases and was always accompanied by lower extremity involvement. Four patients (10%) experienced generalized myalgia and in two cases (5%) paraspinal muscles were involved [16, 25]. Refusal to walk and gait abnormalities occurred in ten (26%) and 11 (28%) patients, respectively. Clinical examination revealed tenderness of affected muscles (74%) as the most frequent finding besides muscle pain. Soft tissue edema was present in five children (13%). Mackay et al. [34] found refusal to walk in 19%, with the remaining 81% showing gait abnormalities. In the reference group, the duration of muscle symptoms ranged from 1 to 30 days (median 3 days). Lundberg [3] and Middleton et al. [4] reported a mean duration of 3 days. Farrell et al. [17] noted that recovery took 3 to five days. CPK was determined in 36 patients listed in the reference group (median 4,100 U/l; range 230– > 106). Overall, CPK was measured in 230 of 311 cases and was elevated in 219 (95%). Serum lac-