Post-influenza neuromuscular complications

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ABSTRACT

According to the data of the World Health Organization, every year influenza develops in up to 1.575 billion people, and 1 million of them die. Although influenza viruses are the leading cause of the upper respiratory tract infections, severe neuromuscular complications occur as well, frequently leading to disability or even death. Children under five years of age and elderly people are at the highest risk of complications and mortality. The article discusses the selected neuromuscular complications of influenza, bringing particular attention to their etiology, symptomatology, diagnostics, and therapy.

Key words: Influenza; Acute encephalopathy; Reye’s syndrome; Guillain-Barré syndrome; Kleine–Levin syndrome; Benign acute childhood myositis

INTRODUCTION

Influenza is an acute infectious disease of the respiratory system evoked by viruses of Orthomyxoviridae family. Like many others, these viral infections can be seasonal, endemic, or even pandemic. According to the data for 2016 by the Polish National Institute of Hygiene, the incidence of influenza in Poland in adult population was 11,233/100,000, of whom 16,648 patients were referred to the hospital. In the population age 0–14, the incidence was 35,399/100,000, of which 9428 were hospitalized. In addition there were 140 deaths in patients with influenza virus confirmed by RT-PCR (1). According to the World Health Organization (WHO), every year influenza occurs in up to 1.575 billion people and 1 million of them die (2).

Based on the antigenic variability of main virion proteins - the M protein and NP nucleoprotein, three virus types: A, B, and C were distinguished. Unique features of the type A such as antigenic drift and antigenic shift contribute to frequent modifications of antigen surface proteins - hemagglutinin (HA) and neuraminidase (NA). Up to now, 11 NA subtypes (N1-N11) and 18 HA subtypes (H1-H18) of the type A influenza virus were isolated. They may infect both humans and animals, and are usually responsible for the development of epidemics and pandemics, with a more severe clinical course. The type B virus is pathogenic only for humans, with milder clinical course. In turn, human or pig infection with the type C virus is, as a rule, an abortive form of the disease. Antigenic variability of the types B and C is of minor clinical importance (3-5).

Infection with influenza virus is most often transmitted by air, less often by skin and everyday use objects that contaminated with infected secretions, by touching ill or dead animals or by eating raw meat or eggs of birds. The clinical picture of the
disease includes symptoms of the upper and lower respiratory tract infections together with general symptoms, such as high fever, shivering, headaches, muscle and joint pain, general weakening, and malaise. Some patients complain of gastric symptoms (3). The majority of uncomplicated influenza cases show a tendency to spontaneous remission within 3–7 days. Although the highest incidence rate is reported in children and young adults, the risk of serious complications as well as the highest mortality is observed in the group of patients over 65 years of age and below 5 years old. Main complications of influenza concern the respiratory system. Unfortunately, rarely occurring but associated with high risk of disability or death, neuromuscular complications are still underestimated. Beside the most frequent complication, such as febrile convulsions, more serious complications occur less frequently an may include acute encephalopathy, Reye's syndrome, Guillain-Barré syndrome (GBS), Kleine–Levin syndrome (KLS), or benign acute childhood myositis (BACM), which will be further discussed in this review (6).

NEUROLOGICAL COMPLICATIONS

Acute encephalopathy
Not only as common as influenza itself but also a much more serious consequence of influenza is acute encephalopathy (influenza-associated acute encephalopathy/encephalitis, [IAE]) that is burdened with a high risk of development of neurological complications and high mortality. It is most often diagnosed in children below five years of age and does not show any gender predilections. Although the majority of cases is registered in Japan during typical influenza epidemic periods, occasional infections also occur in the other parts of the world such as North America, Taiwan, and Europe (7). In the infectious season 1998–1999, Japanese Ministry of Health ordered to conduct a multicenter, cross-sectional study concerning influenza incidence in all the medical facilities. Of 217 IAE cases identified based on the clinical symptoms, 82.6% were children under five years of age (179 children), 58 patients died (26.7%), and neurological complications remained in 56 patients (25.8%) (8). In another national study, Morishima et al. performed a detailed analysis of 148 patients with virologically proven IAE (78 boys and 70 girls). One hundred thirty cases were a result of the type A influenza virus infection (87.8%), whereas type B influenza virus was detected in 17 people. One hundred twenty-one patients were under five years of age (81.8%), mortality fluctuated around 31.8%, and the incidence of neurological complications amounted to 27.7% (9). In the following years, analogical scientific analyses were conducted, whose conclusions were in accordance with presented above (10,11).

Type A (including H1N1 and H5N1), B, as well as type C influenza may cause encephalopathy (7). However, the attitude of scientists concerning the invasiveness of these viruses to central nervous system tissues remains a debate. Only in a small group of patients with IAE virus, RNA was isolated from the cerebrospinal fluid and brain tissue and no histopathological features of inflammation were detected in brain autopsy specimens. On the contrary, the results of some in vitro experiments and animal tests explicitly demonstrate that viruses populate the CNS through peripheral nerves inducing neural infection and encephalopathy, thus contributing to apoptosis of endothelial cells, astrocytes, and neurons (7). In the etiopathogenesis of IAE, the issue of cytokine storm is raised as well. In many scientific works, increased concentration of pro-inflammatory cytokines, i.e., IL-6 or tumor necrosis factor α in plasma and cerebrospinal fluid of patients was observed, and IL-6 level corresponded to the clinical condition and long-term prognosis. The cytokines mentioned above penetrate the blood-brain barrier and damage the vascular endothelium, glia, and neurons causing edema and destruction of the brain tissue. Analogically, in some participants, enhanced synthesis of proapoptotic proteins, i.e., cytochrome c or E-selectin was noted (12). It is worth remembering that hepatogenic or nephrogenic metabolic disorders or coagulopathies such as hypoprothrombinemia or disseminated intravascular coagulation can be triggering factors for IAE (13). What is interesting, genetic predisposition can increase the risk of development of IAE (7). Figure 1 gives a summary of the pathways leading to IAE and associated consequences.

First neurological manifestations of the disease usually appear after two days since the onset of influenza
FIGURE 1. Etiopathogenesis of influenza-associated acute encephalopathy. In some patients with certain genetic background, abnormal hypercytokinemia in response to specific influenza viruses infection is observed. These cytokines penetrate BBB and damage the vascular endothelium, glia, and neurons causing edema and destruction of the brain tissue. Sometimes, viruses populate the CNS through peripheral nerves or damaged BBB inducing cytokine storm and, consequently, neuroinfection with encephalopathy. The above-mentioned cytokine storm may contribute to hepatic or renal dysfunction, metabolic disorder, coagulopathy, and DIC. BBB: blood–brain barrier; DIC: Disseminated intravascular coagulation; CNS (7).
symptoms. Diverse symptomatology of the condition described by Kasai et al. and Morshima et al. includes typical infectious ailments, such as fever, cough, nose secretion, sore throat, and headache that are complicated by convulsions, disorders of consciousness, impairment of cognitive processes, paresis, sensation deficit, deliriant behavior, or mental disorders (7-9).

Establishment of diagnosis is based on clinical and laboratory recognition of influenza and encephalopathy. To do this, a physician can use contemporarily available neuroimaging techniques, i.e., magnetic resonance imaging (MRI), computed tomography (CT), or electroencephalography (EEG). In one of the most interesting studies, in 74.1% of CT (60/81 cases) and 56.7% of MRI (17/30 cases) images, symmetrical pathological areas were observed in the thalamus, pons, and brainstem (10). What is more, the level of advancement of radiological lesions corresponded with the prognosis (7). The most common electroencephalographic abnormalities include, among others, focal slowing, sharp waves in the frontal and temporal leads, and convulsions (7).

In pharmacotherapy, antiviral drugs, i.e., oseltamivir and amantadine are used. In more severe cases, the introduction of anti-cytokine drugs (methylprednisolone and ulinastatin) or even mild hypothermia is worth considering. Four children with severe IAE were subjected to hypothermia to calm the cytokine storm in the CNS. The temperature of their organisms was kept at 34°C for 3 days, and then for three following days, normal organism temperature was restored at the rate not higher than 1°C per day. This management protected the patients from the development of brain edema and severe, sometimes irreversible neuronal changes (14).

Guillain-Barré syndrome
The first descriptions of Guillain-Barré syndrome, an unknown disease until that time, date to the beginning of the 19th century. The disease was described as a sudden, progressive flaccid paralysis of the extremities appearing mainly in young adults and elderly people. Results of intensive studies and follow-up conducted in the following years enabled to classify these cases as acute inflammatory demyelinating polyradiculopathies and call it by the common name of GBS (15). Prevalence of the condition fluctuates around 1.3/100,000 people, with a dominance of male gender (1.25:1). The mechanism of disease is still not clear. It is assumed that bacterial or viral infections induce autoimmune cross-reaction against gangliosides or their combinations in the peripheral nerves GBS (15,16). In 60% of cases, polyneuropathy is preceded by an infectious disease of the respiratory system or gastrointestinal tract occurring 1–3 weeks earlier. Recent research suggests that Campylobacter jejuni may play an important role in the etiopathogenesis of GBS. However, recent literature suggests also influenza viruses as leading players in etiopathogenesis (17). Sporadic descriptions of cases suggesting the association of influenza with GBS were supported by the results of the first epidemiological studies. Multicenter Italian case-control study of GBS in 1996–1998 has shown that the majority patients had symptoms of respiratory tract infection, influenza-like symptoms, or gastrointestinal symptoms two months before the onset of the first neurological symptoms. The authors concluded that, among others, influenza and influenza-like symptoms significantly increased the risk of GBS development in the near future (OR 3.57, \( P = 0.02 \)) (15,18). Similar observations were noted by British researchers, according to whom an influenza-like disease causes a 15-fold increase of the chance of appearing of polyneuropathy in the following 30 days (19). Unfortunately, lack of microbiological or serological confirmation of influenza infection in the analyzed patients is a severe limitation of the above studies. Interestingly, the results of the study by Sivadon-Tardy et al. observed a statistically significant positive numerical correlation between the incidence of GBS and influenza-like infections. Importantly, in 20% of patients with GBS, a recent infection with A or B-type influenza virus was serologically confirmed (20).

An increase in the incidence of GBS in 1976 was associated with the vaccination against swine flu. The incidence observed then was estimated to be 1/100,000 of the vaccinated people, with the dominance of patients age ≥25 years (21). However, until then, no studies were published about relationship between influenza vaccinations and GBS. Quite the opposite, extrapolating the former scientific data, it
can be expected that more probable is that GBS is evoked by influenza virus than by the vaccine that even has a protective action (16,17).

As it has been established so far, there are several subtypes of the disease, i.e., a classical variant that is acute inflammatory demyelinating polyneuropathy (AIDP), Miller-Fisher syndrome, acute motor axonal neuropathy (AMAN), and acute motor and sensory axonal neuropathy (AMSAN). In the beginning, the patients present with non-specific symptoms such as weakening, back pain or neck pain, and paresthesias. Further evolution of the disease leads to symmetrical tetraplegia, sometimes with accompanying weakening of respiratory muscles, facial nerve paresis, and bulbar symptoms that are most strongly felt around the 4th week of the disease. In as much as 56% of cases, polyneuropathy is ascending, at first affecting the lower extremities and then the upper ones. In the majority of patients, all these symptoms undergo partial or total remission within several weeks, months, or years. However, it is worth noting that in the acute phase of the disease, mortality fluctuates around 10%, and 25% of patients require artificial ventilation (15-17).

The suggested diagnostic scheme includes neurophysiological examination, lumbar puncture, a routine blood test, and the anti-ganglioside antibody assay. Therapeutic management depends on the patient’s clinical condition. Life threat in GBS resulting from heart arrhythmia or deteriorating respiratory function requires 24-h monitoring of a patient, often under the ICU conditions. Currently, a gold standard of therapy is treatment with intravenous immunoglobulin at the dose of 0.4 g/kg/24 h for 5 days. Sometimes, 4–6 plasmapheresis treatments are conducted. A slow convalescence process shall be enriched with analgesic therapy, multidirectional rehabilitation, and patient’s education (16).

Reye’s syndrome
Reye’s syndrome is often associated with aspirin and children. This connotation is correct because a statistical correlation was demonstrated for acetylsalicylic acid administered in the prodromal infectious phase, however cause-and-effect relationship was not proved (22). Thus, the Centers for Disease Control and Prevention issued a warning about using aspirin in the infectious respiratory tract diseases in children under 16 years of age (23). However, other factors such as toxins, metabolic disorders, or viral infections including influenza infections are still underestimated in the etiopathogenesis of the said condition. The majority of patients are children over two years old, but the syndrome can also occur in infants and adults. In the previous century, Reye’s syndrome infections were associated regarding time and geography with the type A and B influenza epidemic outbreaks. For example, in the USA during epidemic periods 1973–1974 and 1976–1980, over 2000 cases of Reye’s syndrome were noted and more than 90% of patients were under 15 years of age (17,24). In the next epidemiological analysis conducted between January 1970 and December 1980 in Southwestern Pennsylvania, 97 patients with Reye’s syndrome were identified. In 44 patients (45%), the onset of the condition was identified with the documented influenza epidemic period. The mean age of the infected patients was 9.8 years and 15 patients died (35%) (17,25).

The syndrome itself is as an acute, non-inflammatory encephalopathy that occurs with fatty degeneration of the liver and other internal organs. It is a result of generalized damage and dysfunction of mitochondria. Usually, the course of the disease is biphasic after several days of symptoms of a viral infection, a 3–5-day false recovery appears that is followed by sudden disorders of consciousness, convulsions, and vomiting that are the result of metabolic disorders including hypoglycemia and hyperammonemia. Unfortunately, the prognosis is unfavorable because frequently the disease ends with death or residual neurological complications (17,26).

Kleine-Levin syndrome
Kleine-Levin syndrome also known as “Sleeping Beauty syndrome”, “recurrent hypersomnia and pathological hunger syndrome”, or “periodic sleep disease syndrome” was described for the first time in 1925 by Kleine and then, in 1936, by Levin. It is a rare neurological condition that is characterized by recurrent hypersomnia episodes lasting longer than 18 h and persisting for several days to several weeks. They are accompanied by hyperphagia,
cognitive, and behavioral disorders with excessive sexual excitement. The syndrome concerns mainly boys and men age 10 to 25 years (27). According to the literature, among 168 cases of KLS, the majority were men (114 patients, 68%) and the mean age of the patients was 15 years (range 4 to 82 years). The disease duration was around eight years, with on average seven hypersomnia episodes lasting about ten days and recurring every 3.5 months. KLS lasted longer in women and patients with less frequent episodes of excessive sleepiness during the first year of the disease (28).

An unambiguous attitude concerning the etiology of the above-described condition has not been determined so far. Nevertheless, scientists suggest that it is a result of viral or post-infectious autoimmune encephalitis that impairs the functioning of the hypothalamus or hypophyseal-hypothalamic axis (17,27). Patients who developed post-infectious KLS exhibited a significant association with DQB1*02 haplotype that also supports the autoimmune background of the disease (29). According to Arnulf et al., 72 people of 168 examined patients with KLS (43%) presented with prodromal infectious symptoms or an increase in body temperature, in 42 patients (25%), non-specific or influenza-like fever was observed, whereas 20 patients (12%) suffered from the upper respiratory tract infection, tonsillitis, cough, or a sore throat. An etiological factor was confirmed only in 5 cases (3%), including the infection with Asian influenza virus (28).

In diagnostic management, apart from laboratory analyses and neuropsychological tests, the assessment of brain bioelectrical activity with the use of awake, drowsiness, and sleep EEG has an important place. Chmielik et al. described a 17-year-old patient presenting with recurrent KLS episodes since 15 years old. At the initial EEG examinations, short low-voltage and medium-voltage discharges of groups of sharp wave series were observed. Nevertheless, once the valproic acid therapy had been introduced, normalization of the bioelectric recording was achieved during 11 months (27). It is often worth to extend the diagnostics to neuroimaging examinations, i.e. CT, MRI, and single-photon emission tomography (SPECT). During the KLS episode and two weeks after its symptoms resolved, SPECT examination revealed a pronounced left-side dominant hypoperfusion in the temporal and frontal lobes and the area of the right lateral ventricle in the parietal lobe. What is interesting, the same examination performed seven years after healing indicated an improvement in brain perfusion in frontotemporal area with persisting slight hypoperfusion in the left temporal lobe (30). During the first hypersomnia attack, its other life-threatening causes shall be excluded, including increased intracranial pressure, status epilepticus, metabolic or endocrinological disorders, and drug poisonings (27).

Due to the mild course of the disease and a tendency to spontaneous remissions, many patients do not require the implementation of pharmacotherapy. Nonetheless, alleviation of symptoms and reduction of the frequency of attacks were reported after the administration of lithium salts and in the patients with abnormal EEG recording - after the implementation of valproic acid (27).

MUSCULAR COMPLICATIONS

Benign acute childhood myositis

In 1957 Swedish physician Lunberg for the first time described a muscular disease - Myalgia Cruris Epidemica, currently known as benign acute childhood myositis (BACM). Since that time, many individual cases and even foci of epidemics were registered worldwide. The said inflammation, every time preceded by fever lasting for several days and catarrhal symptoms, begins with a sudden, bilateral strong calf muscle pain that hinders or even prevents walking, accompanied by their excessive tenderness to palpation. What is important, exteroceptive sensation, deep reflexes, muscle tone, and strength are normal. Sometimes one of the two pathological gait patterns is observed: Walking on toes (the so-called “toe walking”) or stiff, broad-based walking. This condition most often affects early school-age children, predominantly boys. A predilection for male gender is explained by greater physical activity, genetic predisposition, or previously undiagnosed metabolic disorder (6,31). Although etiopathogenesis of BACM is not fully known, the most probable hypothesis is an inflammatory process with immunological background induced by an infection - most often viral one (31). It is proved by the more frequent
occurrence of BACM in late winter and early spring period that explicitly suggests a cause-and-effect relationship of the inflammation with respiratory tract infections (32). The main pathogens that are responsible for the described condition are A and B-type influenza viruses. Sporadically parainfluenza viruses, herpes simplex, Epstein–Barr, Coxsackie, RSV viruses, adenov-, entero-, and rota-viruses, dengue virus, or Mycoplasma pneumoniae contribute to the development of the disease (6,33). The outbreak of the type B influenza in Germany in the season 2007/2008 forced the hospitalization of 219 children with BACM. The majority of them was boys (74%, 160/216 patients), and the mean age at the onset was seven years (34).

Similarly, boys (mean age 7.3 years) were dominant (43/54, 80%) in suspected BACM, admitted to the Pediatric Departments in Tel-Aviv and Jerusalem in 2010–2013. The virological test was conducted in 21 patients and its result was positive for the type A influenza virus in two cases and for the type B influenza virus in one case (35). Analogical conclusions were presented by Portuguese researchers who analyzed 28 cases of children treated for BACM in 2001–2012. Eighty-four percent (21) were boys aged from 4 to 10 years (mean age 7 years). In 20 cases, serological tests were conducted with two positive results for the type A influenza virus and one positive result for the type B influenza virus (33). Contrary to the predecessors, Greek researchers noticed only a slight BACM predilection to male gender (18 boys vs. 14 girls) that would deny the previously raised hypothesis concerning the genetic predisposition of boys to the above disease (36). It is assumed that BACM develops only during the first contact with the virus that explains a limited number of cases described in adults (37).

Biochemical disorders observed in laboratory tests include, above all, high creatine phosphokinase (CPK) concentration, sometimes reaching values 20–30-fold above the accepted range. For example, in Portuguese studies, the mean CPK value fluctuated around 4181 UI/L (range from 785 to 26863 UI/L), in Israeli studies - around 1872 IU/L (range from 511 to 8086 UI/L), and in Greek studies - around 2850 UI/L (range from 558 to 6800 UI/L) (33,35,36). However, acute rhabdomyolysis is not usually observed (37). Nevertheless, this uncommon but severe complication, whose symptoms include dark-colored urine and a positive result of urine test strip analysis indicating the presence of blood in urine with simultaneous absence of red blood cells in the microscopic analysis, should be taken into account. An increase in plasma transaminase (especially, aspartate transaminase [AST]) as well as lactate dehydrogenase concentration, leucopenia, neutropenia, and thrombocytopenia, often with simultaneous normal values of the markers of inflammation such as CRP or erythrocyte sedimentation rate, was also described. The result of the electromyographic examination is usually within normal limits or exhibits short motor units (<3 ms) with low amplitude (<300 UV) irregularly distributed in several muscles in the upper and lower extremities (38). Sometimes increased signal intensity in T2-weighted images, more clearly indicated in STIR sequence, is observed in MRI and it concerns muscles affected by the disease (39). Muscle biopsies are rarely performed due to short-lasting symptoms and good prognosis, and they do not show any pathologies typical for BACM or demonstrate slight necrosis and regeneration of muscle fibers with the features of interstitial edema and inflammatory infiltrates (38). Summary of clinical and laboratory characteristics of children with BACM is shown in Table 1.

In case of the presence of family history of neuromuscular diseases, a recent injury or excess physical exercise, myoglobinuria, subacute or chronic course, newly formed rash, excessively weakened muscle strength, or other abnormalities in neurological examination during the diagnostic process, a physician is obliged to exclude such severe conditions as rhabdomyolysis, GBS, primary inflammatory myopathies, muscular dystrophies, or metabolic disorders (33).

Normalization of clinical and laboratory parameters of this self-limiting condition occurs within several days, so the mean hospitalization period lasts three days (from 1 to 7 days). Symptomatic treatment mainly analgesic drugs, intravenous hydration, and resting in bed - is supportively implemented. It does not seem that NA inhibitors are effective due to BACM development in the late phase of influenza, so they are not indicated. Many patients do not
require admission to the hospital, and their treatment is restricted to the outpatient supervision. The disease does not leave behind any complications. Recurrences are rare and are caused by another virus or a different type of influenza (33).

Physicians who deal with young patients on a daily basis shall remember about this rare disease that can complicate such common influenza infections. As in the differential diagnosis of BACM, diseases with unfavorable prognoses are taken into account; only a competent diagnosing will enable to save both the child and the parents from the stress associated with unnecessary and often uncomfortable diagnostic procedures.

CONCLUSION

Acute encephalopathy, Reye’s syndrome, Guillain-Barré syndrome (GBS), Kleine–Levin syndrome (KLS), and benign acute childhood myositis (BACM) are less frequent but potentially severe neuromuscular complications caused by influenza viruses. Vaccination against influenza is one way of preventing such complications. Although in many independent studies the effectiveness of anti-influenza vaccines ranges from 50% to 70%, their usage in Poland is rather low, such as in the epidemic season 2012/2013, where vaccination level was 3.75% (40). Therefore, raising of awareness of public is necessary to increase vaccination levels, thus reducing incidence of the severe complications as well as economic costs of the disease.

REFERENCES


**TABLE 1. Summary clinical characteristics of children with BACM**

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<td>Total number of patients</td>
<td>25</td>
<td>54</td>
<td>32</td>
<td>9</td>
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<tr>
<td>Sex - male, n (%)</td>
<td>21 (84)</td>
<td>43 (60)</td>
<td>14 (43.75)</td>
<td>5 (55.55)</td>
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<tr>
<td>Sex - female, n (%)</td>
<td>4 (16)</td>
<td>11 (20)</td>
<td>18 (56.25)</td>
<td>4 (44.44)</td>
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<td>4-12.5</td>
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<td>Mean age (years)</td>
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<td>7.3</td>
<td>6.3</td>
<td>7.3</td>
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<td>Myalgia, n (%)</td>
<td>25 (100)</td>
<td>44 (81)</td>
<td>30 (93.8)</td>
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<td>Fever, n (%)</td>
<td>NA</td>
<td>39 (72)</td>
<td>13 (40.6)</td>
<td>9</td>
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<td>Hospitalization, n (%)</td>
<td>25</td>
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<td>Duration of hospitalization (days)</td>
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<td>511-8086</td>
<td>558-6800</td>
<td>216-9860</td>
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<td>2207</td>
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<td>63-145</td>
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<td>59-1070</td>
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<td>15-113</td>
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<td>21 (39)</td>
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<td>9 (100)</td>
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<td>Viral studies positive for influenza virus, n (%)</td>
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*BACM: Benign acute childhood myositis; n: Number; WBC: White blood cells; AST: Asparagine aminotransferase; ALT: Alanine aminotransferase; NA: Not available


