

Benign acute childhood myositis complicating influenza B infection in a boy with idiopathic nephrotic syndrome

PIOTR SKRZYPCZYK, JOANNA PRZYCHODZIEN, MAŁGORZATA PAŃCZYK-TOMASZEWSKA

Department of Pediatrics and Nephrology, Medical University of Warsaw, Poland

Abstract

Introduction: Benign acute childhood myositis (BACM) is an acute complication of an infection characterized by calf pain, limitation of lower limb mobility, an increase in serum creatine kinase, and a self-limiting course. No reports of BACM in children with idiopathic nephrotic syndrome (INS) can be found in the literature.

Case report: A 5-year-old boy with steroid-sensitive INS presented with fever, leg pain, and problems with walking. Physical examination showed pharyngeal erythema, preserved movements in all joints, and weakness of leg muscles. Laboratory tests showed white blood cell count 3900/ μ l, albumin 2.3 g/dl, urea 25 mg/dl, creatinine 0.3 mg/dl, increased transaminases (AspAT 440 U/l, AlAT 100 U/l) and creatine kinase (10 817 U/l), and proteinuria 3500 mg/dl. The boy was diagnosed with an INS bout and BACM. Testing for infective causes of myositis showed evidence of an influenza B virus infection. Treatment included prednisone and oseltamivir. A rapid improvement of motor function was observed, with normalization of serum creatine kinase and transaminases, and resolution of proteinuria.

Conclusions: 1. As influenza virus infection in a child with INS is a risk factor for complications and a disease bout, these patients should be vaccinated against influenza. 2. Differential diagnosis of leg pain and mobility limitation in a child with INS should include lower limb deep venous thrombosis, arthritis, post-infectious neurological complications (including Guillain-Barré syndrome), and BACM. 3. Serum creatine kinase level should be measured in all cases of motor disturbances in a child with symptoms of respiratory tract infection.

Key words: children, nephrotic syndrome, benign acute childhood myositis.

(*Cent Eur J Immunol* 2016; 41 (3): 328-331)

Introduction

Nephrotic syndrome is characterized by nephrotic range proteinuria (defined as urine protein : creatinine ratio \geq 2000 mg/g) and hypoalbuminemia (serum albumin level \leq 2.5 g/dl), most commonly associated with hyperlipidemia and edema [1]. The most common cause of nephrotic syndrome in the pediatric population is idiopathic nephrotic syndrome (INS), present in 90% of children with nephrotic syndrome diagnosed between 1 and 10 years of age and in 50% of children with the diagnosis made at the age of $>$ 10 years [2, 3]. Infections, particularly viral infections of the airways, are common factors precipitating the initial and recurrent bouts of the disease.

Influenza is an acute airway disease caused by an infection with influenza A or B virus, an RNA virus of the *Orthomyxoviridae* family. A high risk of influenza complications is seen in certain groups including children, par-

ticularly below 2 years of age, subjects $>$ 65 years of age, patients with chronic disease (including kidney disease), those receiving immunosuppressive treatment, and obese subjects [4]. Complications include dehydration, otitis media, pneumonia, croup, bronchitis or less commonly bronchiolitis, myelitis, encephalitis, and aseptic meningitis, Guillain-Barré syndrome, seizures (including febrile), secondary bacterial infection, most commonly with *Staphylococcus aureus* [5], and myocarditis. Myopathy, including influenza-associated benign acute childhood myositis (IA-BACM), is found in up to 33.9% of influenza B cases and 5.5% of influenza A cases [6].

The aim the article is to draw attention to possible complications in children with idiopathic nephrotic syndrome illustrated by the example of a case of benign acute childhood myositis in the course of influenza B in a boy with idiopathic nephrotic syndrome.

Correspondence: Piotr Skrzypczyk, Department of Pediatrics and Nephrology, Medical University of Warsaw, Żwirki i Wigury 63 A, 02-091 Warsaw, Poland, e-mail: pskrzyp@gmail.com

Submitted: 23.06.2016; Accepted: 09.09.2016

Case report

A 5-year-old boy with steroid-sensitive INS was admitted to a hospital due to fever, leg pain, and difficulties with walking.

The initial bout of INS occurred at the age of 2 years and 4 months. Before the present hospitalization, 4 bouts of the disease occurred (including 2 complicating an airway infection, one following allergen exposure, and one without a discernible cause). The patient was treated with prednisone only, and did not receive glucocorticosteroids for the last 4 months.

History taking revealed fever up to 38.6°C at 3 days before admission, with resolution of fever on the next day, followed by symmetrical leg pain, and the boy stopped walking due to pain. On admission, evidence of viral pharyngitis was found on the physical examination. Skin of the lower limbs was not affected, there was no limb edema including joint swelling, and no generalized edema was found. On neurological examination, normal muscle strength and tone were found, lower limb motor reflexes were symmetrical and brisk, and no pyramidal or extrapyramidal signs were found, consistent with no evidence of a neurological cause of the symptoms. Laboratory tests showed a decreased white blood cell count (3900/mm³) with neutropenia (1400/mm³), normal hemoglobin level (12.8 g/dl), and normal platelet count (226,000/mm³), elevated transaminase level with an increased AspAT (aspartate transaminase) : AlAT (alanine transaminase) ratio (AspAT 440 U/l, AlAT 100 U/l), markedly elevated creatine kinase (CK) level (10817 U/l, reference range 30-150 U/l), hypoalbuminemia (total protein 4.9 g/dl) with hypoalbuminemia (albumin 2.3 g/dl), hypertriglyceridemia (306 mg/dl) with normal total cholesterol level (150 mg/dl), normal C-reactive protein (CRP) level (< 0.5 mg/dl), normal renal function parameters (creatinine 0.3 mg/dl, urea 24 mg/dl), and normal electrolytes (sodium 138 mmol/l, potassium 4.5 mmol/l). Coagulation parameters included normal international normalized ratio (INR 1.00), slightly increased activated partial thromboplastin time (42.66 s, reference range 28-40 s), normal fibrinogen level (2.87 g/l), and slightly increased D-dimer level (1723.12 µg/l). All tests for autoimmune inflammatory connective tissue disorders were within normal limits [C3 – 122 mg/dl (reference

range 88-165 mg/dl), C4 – 41.4 mg/dl (14-44 mg/dl), total IgA 173.9 mg/dl (38-235 mg/dl), IgM 123.6 mg/dl (36-198 mg/dl), rheumatoid factor < 8.6 IU/ml (< 12 IU/ml), antistreptolysin O < 25 IU/ml (< 200 IU/ml), antinuclear and anti-neutrophil cytoplasmic antibodies (both negative)] except for lowered total IgG level – 502.3 mg/dl (853-1440 mg/dl). Urinalysis revealed yellow urine with proteinuria 3500 mg/dl and erythrocyturia 4-6 per field of view. Lower limb imaging studies (X-ray and ultrasonography, including Doppler evaluation) showed no abnormalities. Due to the high CK level, testing for infective causes of myositis was performed, showing evidence of influenza B virus infection (nasopharyngeal swab, PCR RNA testing), and acute Epstein-Barr virus, cytomegalovirus, *Chlamydomphila pneumoniae*, and *Mycoplasma pneumoniae* infection was excluded by serological testing. Treatment included prednisone 60 mg/m²/24 hours (started on the first day of the hospital stay) and oseltamivir 45 mg twice daily (started on the second day of the hospital stay following confirmation of the influenza virus infection and continued for 5 days). A rapid improvement of the symptoms of airway infection and motor function was observed, with reduction of serum creatine kinase, transaminase levels, and proteinuria (Table 1). Proteinuria resolved on the eighth day of the hospital stay.

Discussion

Lower limb pain in a child with nephrotic syndrome is always an alerting symptom and requires extensive diagnostic work-up.

Taking into account multiple risk factors for thrombotic complications in children with INS (hemoconcentration, increased platelet count and activity, urinary loss of coagulation inhibitors including plasminogen, antithrombin III, and C and S proteins, hyperfibrinogenemia, reduced plasminogen activator activity [7]), lower limb venous thrombosis should be excluded [8, 9]. In the reported case, thrombosis might have been suggested by an elevated D-dimer level, but the clinical presentation was not consistent with this diagnosis (bilateral leg pain, no edema and lower limb skin discoloration), and Doppler ultrasound was normal.

Table 1. Selected biochemical parameters in a boy with idiopathic nephrotic syndrome and benign acute childhood myositis complicating an influenza B virus infection

Parameter	Days of hospital stay			
	1	3	7	8
CK [U/l]	10 817	1079	47	–
AspAT [U/l]	440	216	28	–
AlAT [U/l]	100	103	40	–
Proteinuria [mg/dl]	3500	130	36	0

CK – creatine kinase; AlAT – alanine transaminase; AspAT – aspartate transaminase

Due to concomitant symptoms of an airway infection, the differential diagnosis needed to include post-infectious neurological complications. Neurological examination showed normal muscle strength and tone, symmetrical, brisk lower limb motor reflexes, and no pyramidal or extrapyramidal signs, and thus it did not indicate any neurological disease including Guillain-Barré syndrome, post-infectious cerebellar ataxia, or neuroinfection. Differential diagnosis of acute motor disturbances also includes arthritis including juvenile idiopathic arthritis, dermatomyositis, muscle dystrophies, trichinosis, steroid-induced avascular necrosis of the femoral head, and posttraumatic changes.

Clinical manifestations together with normal findings of the knee and hip X-ray and ultrasonography together with a high CK level (10 817 U/l) indicated that the patient's complaints were related to myositis and not arthritis. We looked for infective causes of myositis, and a nasopharyngeal swab for influenza was performed, confirming influenza B virus infection. Thus, the diagnosis of IA-BACM was made.

Benign acute childhood myositis was first described by Lundberg in 1957 under the name of myalgia cruris epidemica [10]. The disease is characterized by an acute pain in the affected muscles (mostly calf muscles) with motor impairment. Pain increases with limb dorsiflexion [11-13]. This complication is twice as common in boys, usually aged 6-9 years [11, 14, 15]. A genetic predisposition to IA-BACM may exist, as evidenced by recurrences reported in the literature [11, 12] and disease occurrences in siblings [11, 12]. Myositis more frequently complicates influenza B than A. Hu *et al.* reported this complications in as many as 33.9% of children with influenza B and 5.5% of children with influenza A [6]. Initial symptoms usually occur 3 days (range 0-18 days) after the first symptoms of influenza [14]. Management of BACM includes rest and non-steroidal anti-inflammatory drugs [11].

Myositis may also complicate other viral infections including herpes [16], enterovirus [17], HIV [18], measles [19], Dengue virus [13], and even *Mycoplasma pneumoniae* infection [20]. It is also believed that use of immunostimulant drugs including inosine pranobex [11, 21] may be a predisposing factor. Muscle biopsy shows degenerative changes, focal myofibril vacuolization, and myonecrosis [13]. Postulated mechanisms of muscle damage include direct microorganism invasion into myocytes, damage induced by viral toxins, and immune reactions caused by cytokine storm [22]. Desdouits *et al.* observed the presence of sialic acid receptors on skeletal muscle cells. Using these receptors, influenza virus penetrates airway epithelial cells. The same authors also reported viral replication in rhabdomyocytes with resultant cell destruction [23].

The disease is characterized by a self-limiting course and a typical configuration of biochemical parameters, including elevated creatine kinase and transaminase levels with normal inflammatory parameters [11]. Creatine

kinase and aspartate transaminase levels seen in our patient are among the highest reported in the literature in BACM cases [12, 24-26].

Although most cases of IA-BACM are characterized by a mild, self-limiting course, the disease may sometimes lead to massive rhabdomyolysis (3% of IA-BACM cases) manifesting with myoglobinuria and renal failure (80% of patients with rhabdomyolysis). Rhabdomyolysis is more common in girls (80%) and in influenza A (86%) [14].

Children with INS are characterized by a high risk of infective complications. Factors predisposing to infections in this patient group include urinary loss of IgG immunoglobulins and complement factors B, D, and I [27-29], T cell function abnormalities [30], particularly involving regulatory T cell (Treg) subpopulations [31], and immunosuppressive treatment used in these patients. Reports of severe influenza virus infections in children with INS were published in the literature [32], but IA-BACM was not reported in these patients. It has also been known for a long time that viral infections, including influenza A, may induce disease bouts in these patients [33]. On the other hand, Kimata *et al.* reported a case of disease remission induced by influenza B virus in a 5-year-old boy with an initial bout of INS [34]. The authors believed that remission was associated with viral stimulation of Treg cells [34], as shown by cytometry.

According to the 2016 immunization schedule in Poland, immunization against influenza is recommended in children with recurrent nephrotic syndrome [35]. Poyrazoğlu *et al.* reported that influenza A vaccination effectively induced protective antibody titers in this patient group [36]. Although it is known that INS bouts may occur following immunization [37], the authors found no association between influenza vaccination and the rate of disease recurrence [36].

In the reported case, INS present in our patient prompted us to initiate specific antiviral therapy with oseltamivir. Moon *et al.* described 5 patients with myositis complicating influenza B virus infection, 4 of whom were treated with oseltamivir without any complications [38]. Currently, there is no clear evidence of benefits of oseltamivir therapy in the case of neurological or muscle complications. Use of oseltamivir combined with full-dose prednisone allowed rapid remission in the reported patient.

Conclusions

As influenza virus infection in a child with INS is a risk factor for complications and a disease bout, these patients should be vaccinated against influenza.

Differential diagnosis of leg pain and mobility limitation in a child with INS should include lower limb deep venous thrombosis, arthritis, post-infectious neurological complications (including Guillain-Barré syndrome), and BACM.

Serum creatine kinase level should be measured in all cases of motor disturbances in a child with symptoms of respiratory tract infection.

The authors declare no conflict of interest.

References

1. Kidney Disease: Improving Global Outcomes (KDIGO) Glomerulonephritis Work Group (2012): KDIGO Clinical Practice Guideline for Glomerulonephritis. *Kidney Int Suppl* 2: 139-274.
2. Lombel RM, Hodson EM, Gipson DS; Kidney Disease: Improving Global Outcomes (2013): Treatment of steroid-resistant nephrotic syndrome in children: new guidelines from KDIGO. *Pediatr Nephrol* 28: 409-414.
3. A report of the International Study of Kidney Disease in Children (1978): Nephrotic syndrome in children: prediction of histopathology from clinical and laboratory characteristics at time of diagnosis. *Kidney Int* 13: 159-165.
4. Centers for Disease Control and Prevention (CDC) (2013): Prevention and control of seasonal influenza with vaccines. Recommendations of the Advisory Committee on Immunization Practices-United States, 2013-2014. *MMWR Recomm Rep* 62: 1-43.
5. Dawood FS, Chaves SS, Pérez A, et al.; Emerging Infections Program Network (2014): Complications and associated bacterial coinfections among children hospitalized with seasonal or pandemic influenza, United States, 2003-2010. *J Infect Dis* 209: 686-694.
6. Hu JJ, Kao CL, Lee PI, et al. (2004): Clinical features of influenza A and B in children and association with myositis. *J Microbiol Immunol Infect* 37: 95-98.
7. Singhal R, Brimble KS (2006): Thromboembolic complications in the nephrotic syndrome: pathophysiology and clinical management. *Thromb Res* 118: 397-407.
8. Egli F, Elmiger P, Stalder G (1973): Thrombosis as a complication of nephrotic syndrome. *Helv Paediatr Acta* 30 (Suppl): 20-21.
9. Kerlin BA, Blatt NB, Fuh B, et al. (2009): Epidemiology and risk factors for thromboembolic complications of childhood nephrotic syndrome: a Midwest Pediatric Nephrology Consortium (MWPNC) study. *J Pediatr* 155: 105-110.
10. Lundberg A (1957): Myalgia cruris epidemica. *Acta Pediatr* 46: 18-31.
11. Hozyasz KK, Gryglicka H, Radomska B (2009): Benign acute childhood myositis (BACM) – cases report. *Pol Merkur Lekarski* 27: 129-131.
12. Mackay MT, Komberg AJ, Shield LK, Dennett X (1999): Benign acute childhood myositis: laboratory and clinical features. *Neurology* 53: 2127-2131.
13. Rajajee S, Ezhilarasi S, Rajarajan K (2005): Benign acute childhood myositis. *Indian J Pediatr* 72: 399-400.
14. Agyeman P, Duppenhaler A, Heining U, Aebi C (2004): Influenza-associated myositis in children. *Infection* 32: 199-203.
15. Mall S, Buchholz U, Tibussek D, et al. (2011): A large outbreak of influenza B-associated benign acute childhood myositis in Germany, 2007/2008. *Pediatr Infect Dis J* 30: 142-146.
16. Schlesinger JJ, Gandara D, Bensch KG (1978): Myoglobinuria associated with herpes-group viral infections. *Arch Intern Med* 138: 422-424.
17. Meshkinpour H, Vaziri ND (1982): Association of myoglobinuria with adenovirus infection. *West J Med* 137: 130-132.
18. Guillaume MP, Van Beers D, Delforge ML, et al. (1995): Primary human immunodeficiency virus infection presenting as myopericarditis and rhabdomyolysis. *Clin Infect Dis* 21: 451-452.
19. Seibold S, Merkel F, Weber M, Marx M (1998): Rhabdomyolysis and acute renal failure in an adult with measles virus infection. *Nephrol Dial Transplant* 13: 1829-1831.
20. Belardi C, Roberge R, Kelly M, Serbin S (1987): Myalgia cruris epidemica (benign acute childhood myositis) associated with *Mycoplasma pneumoniae* infection. *Ann Emerg Med* 16: 579-581.
21. Chuck AJ, Lloyd Jones JK, Dunn NA (1988): Is inosine pranobex contraindicated in autoimmune disease? *Br Med J (Clin Res Ed)* 296: 646.
22. Fadila MF, Wool KJ (2015): Rhabdomyolysis secondary to influenza A infection: a case report and review of the literature. *N Am J Med Sci* 7: 122-124.
23. Desdouts M, Munier S, Prevost MC, et al. (2013): Productive infection of human skeletal muscle cells by pandemic and seasonal influenza A(H1N1) viruses. *PLoS One* 8: e79628.
24. Karpathios T, Kostaki M, Drakonaki S, et al. (1995): An epidemic with influenza B virus causing benign acute myositis in ten boys and two girls. *Eur J Pediatr* 154: 334-336.
25. Sonmez F, Cakir M, Yayla S, Boz C (2004): Benign acute childhood myositis. *Med Princ Pract* 13: 227-229.
26. King BA (2003): Benign acute childhood myositis as a cause of failure to weight bear. *J Paediatr Child Health* 39: 378-380.
27. Matsell DG, Wyatt RJ (1993): The role of I and B in peritonitis associated with the nephrotic syndrome of childhood. *Pediatr Res* 34: 84-88.
28. Spika JS, Halsey NA, Fish AJ, et al. (1982): Serum antibody response to pneumococcal vaccine in children with nephrotic syndrome. *Paediatrics* 69: 219-223.
29. Yetgin S, Gur A, Saatci U (1980): Non-specific immunity in nephrotic syndrome. *Acta Paediatr Scand* 69: 21-24.
30. Shalhoub RJ (1974): The pathogenesis of lipoid nephrosis: a disorder of T-cell function. *Lancet* 2: 556-560.
31. Araya C, Diaz L, Wasserfall C, et al. (2009): T regulatory cell function in idiopathic minimal lesion nephrotic syndrome. *Pediatr Nephrol* 24: 1691-1698.
32. Fujinaga S, Hara T (2015): Acute kidney injury following plastic bronchitis associated with influenza B virus in a child with nephrotic syndrome. *Indian Pediatr* 52: 523-525.
33. MacDonald NE, Wolfish N, McLaine P, et al. (1986): Role of respiratory viruses in exacerbations of primary nephrotic syndrome. *J Pediatr* 108: 378-382.
34. Kimata T, Tsuji S, Kino J, et al. (2013): Close association between proteinuria and regulatory T cells in patients with idiopathic nephrotic syndrome. *Pediatr Nephrol* 28: 667-669.
35. <http://gis.gov.pl/images/ep/akt-1pso2016.pdf>
36. Poyrazoğlu HM, Düşünsel R, Gündüz Z, et al. (2004): Antibody response to influenza A vaccination in children with nephrotic syndrome. *Pediatr Nephrol* 19: 57-60.
37. İşlek I, Cengiz K, Cakir M, Küçüködük S (2000): Nephrotic syndrome following hepatitis B vaccination. *Pediatr Nephrol* 14: 89-90.
38. Moon JH, Na JY, Kim JH, et al. (2013): Neurological and muscular manifestations associated with influenza b infection in children. *Pediatr Neurol* 49: 97-101.