*Case Report*

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# Nephrotic Syndrome Following H1N1 Influenza in a 3-Year-Old Boy

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## Abstract

***Background:*** The pandemic influenza A/H1N1, spread through the world in 2009, producing a serious epidemic in Italy. Complications are generally limited to patients at the extremes of age (<6 months or >65 years) and those with comorbid medical illness. The most frequent complications of influenza involve the respiratory system.

***Case Presentation:*** A 3-year-old boy with a recent history of upper respiratory tract infection developed a nephrotic syndrome. Together with prednisone, furosemide and albumin bolus, a therapy with oseltamivir was started since the nasopharyngeal swab resulted positive for influenza A/H1N1. Clinical conditions and laboratory findings progressively improved during hospitalization, becoming normal during a 2 month follow up.

***Conclusion:*** The possibility of a renal involvement after influenza A/H1N1 infection should be considered.

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***Key Words:*** Influenza A; H1N1; Nephrotic Syndrome; Oseltamivir; Prednisone

## Introduction

In April 2009, a novel influenza A/H1N1 virus was identified in Mexico and extended rapidly worldwide thanks to its genetic and antigenic features resulting in a high incidence of infection, through person to person spread of respiratory secretions[1,2]. Many pediatric patients have visited emergency departments and physicians' offices during this 2009-2010 flu season in Italy.

Clinical presentation of the novel influenza A/H1N1 is similar to those of the seasonal influenza but serious complications have been described[3]. Renal involvement was previously reported in only one case[4]. We report the second patient with nephrotic syndrome (NS) following an upper respiratory tract infection. Real time polymerase chain reaction (RT-PCR) resulted positive for influenza A/H1N1.

## Case Presentation

In November 2009, a 3-year-old boy presented to our Emergency Department with a 4 day history of progressive feet, legs and periorbital edema. Together with edema, his body weight increased from 14.3 Kg to 17.2 Kg. Medical history included

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recurrent urinary tract infections and two weeks earlier an upper respiratory tract infection, characterized by cough, sore throat, and nasal congestion, spontaneously solved in 3 days.

Physical examination showed remarkable finding of generalized anasarca. Blood pressure was normal. Initial urine analysis showed heavy proteinuria (6.67 g/l), confirmed by the 24-hour urine collection which showed a concentration of protein of 8.5 g/l. Other laboratory findings included hypoproteinemia (4,8 g/dl), low serum albumin (2.0 g/dl), hypercholesterolemia (440 mg/dl), elevated low-density lipoprotein cholesterol (238 mg/dl) and hypertriglyceridemia (230 mg/dl). Urinary sediment showed mild microhematuria (6-10 erythrocytes per field) and rare granulated cylinders. The nasopharyngeal swab was taken.

Tests including C3 and C4 complement levels, C-reactive protein, serum creatinine, blood urea nitrogen were normal or undetectable. The clearance of the creatinine at the time of diagnosis was 111 ml/min.

RT-PCR over the nasopharyngeal swab was performed since he reported respiratory symptoms and since influenza A/H1N1 was epidemic in Italy in that season; it resulted positive for influenza A/H1N1.

NS was treated with fluid restriction, low sodium diet and prednisone 60mg/$m^2$ per os daily. Blood pressure, body weight and water balance were daily monitored. Since serum albumin decreased (1.3 g/dl), an infusion of 50 ml of albumin 25% was given, followed by an intravenous bolus of 17 mg furosemide. Interestingly, 24 hours later, the patient was noted to have an increase of the periorbital edema and developed bilateral scrotal hydrocele. Nasopharyngeal swab was positive for influenza A/H1N1 virus and a therapy with oseltamivir 60 mg twice daily was also started.

Over the next 48 hours, the patient achieved significant clinical improvement of his anasarca-related symptoms. Laboratory tests executed after 10 days of corticosteroid therapy showed increasing serum proteins (6.2 g/dl) and serum albumin (3.5 g/dl), together with a concentration of proteins lower than 0.07 g/l in the 24-hour urine collection. Weight at discharge was 14.400 Kg. According to the latest guide-line on the management of childhood onset NS, treatment with prednisone was reduced to 40 mg/$m^2$ on alternate days after 6 weeks and prolonged for further 6 weeks, then suspended without tapering[5]. Clinical conditions and laboratory tests at suspension were normal and no side effects of corticosteroid therapy were reported.

Clinical and laboratory follow-up performed monthly for the first 3 months and than at 6 and 12 months after discharge showed no relapse of NS or respiratory complications.

## *Discussion*

NS is a glomerulopathy characterized by a massive albuminuria, which can be associated with two main types of glomerular lesions, minimal change disease (MCD) and focal and segmental glomerular sclerosis (FSGS). First injury occurs at the level of glomerular podocytes. These cells are highly differentiated visceral epithelial cells whose intercellular space is defined by the slit diaphragm, composed of amolecular complex essential for the maintenance of glomerular permselectivity[6]. The glomerular permeability factor-producing cell is still unknown, but several clinical arguments suggest T lymphocyte involvement, since NS can arise during an activation of the immune system triggered by a viral infection, such hepatitis C and parvovirus B19[7,8]. Respiratory viruses are related to exacerbations and relapse of both MCD and FSGS[9]. The etiology of NS is in most (~90%) cases idiopathic and in the remaining 10% associated with well-defined diseases (such as genetic disorders, multisystem syndromes, metabolic disorders, infections, drugs, immunologic or allergic disorders, association with malignant disease)[10]. We believe that this percentage is bound to fall in the future when we will be able to demonstrate the underlying causes of this disease.

The diagnosis of influenza A/H1N1 is possible by either RT-PCR and/or by viral culture[11]. The preferred specimen is a nasopharyngeal swab, nasal aspirate, or combined nasopharyngeal swab with oro-pharyngeal swab. RT-PCR is the gold standard, with its high sensitivity and specificity.

Sensitivity is $10^3$ to $10^6$ times higher than Enzyme-Linked ImmunoSorbent Assay and cell culture and does not vary with age. Moreover, it is possible to isolate the virus even several days after the symptomatic period[12].

Antiviral medication is the stronghold of therapy for influenza. So, treatment with oseltamivir or zanamivir is recommended for all patients with severe illness thought to be secondary to novel H1N1[13].

Historically, complications are generally limited to patients at the extremes of age (<6 months or >65 years) and those with comorbid medical illness. The most frequent serious complications of influenza are pulmonary and include primary viral pneumonia and secondary bacterial pneumonia, attributable also to unusual pathogens[14]. In addition to its respiratory effects, the virus can exert direct and indirect effects on other body systems.

Myositis and rhabdomyolysis have been noted. In fact, elevations of creatine phosphokinase (CPK) have been reported among patients hospitalized with H1N1[3].

Neurological complications, like altered mental status, encephalopathy and seizures, related with influenza A/H1N1 infection, have been pointed out in children aged 7 to 17 years[15]. Renal involvement after influenza A/H1N1 infection in children has been reported only once in literature[4]. Our case is similar to that of L. Hill et al report: both children developed NS after presenting respiratory symptoms. Subsequently their viral PCR swab resulted positive for influenza A/H1N1 virus. In both cases the prognosis was good at short distance. In our case, the long-term follow-up was negative for relapse. In the treatment there were no deep differences but we added oseltamivir according to the recommended drugs for influenza A/H1N1[13].

Our case seems to be the second report of a NS associated with an infection by the novel influenza A/H1N1 virus. The correlation between the two diseases is evident since the patient experienced an upper respiratory infection before the onset of the NS and the nasal swab resulted positive for H1N1 contemporary to the renal manifestations. No renal biopsy was performed since it was the first episode of NS, but the early and full response of our patient to the corticosteroid therapy suggested that it could have been a case of MCD.

## Conclusion

Our goal is to point out the correlation between influenza A/H1N1 infection and the onset of NS. This is not the first case described since this correlation in the literature has been already mentioned.

Considering that infections are one of the possible causes of NS and taking count of the previous case in the literature, we think that the chronological correlation and laboratory findings are two strong reasons for the causative effect of influenza virus on NS in this patient.

Moreover, our experience suggests that regular management of NS associated with the antiviral drug oseltamivir was efficient and safe in treating both conditions simultaneously.

We believe these observational studies can improve our knowledge about NS.

**Transparency declaration**
No extra funding was used for this case report as data were generated as part of clinical activities. There is no commercial relationship or any potential conflict of interest of any nature.

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