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H1N1 infection and the kidney in critically ill patients

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Abstract

Background: **Acute renal failure due to viral infections is rare. We assessed the development of acute kidney injury (AKI) in critically compromised patients due to the H1N1 influenza virus.**

Methods: **All patients with a PCR-confirmed diagnosis of H1N1 influenza infection admitted to the intensive care unit between May and July 2009 were retrospectively studied. Thereafter, the risk factors associated with the development of acute renal injury, the requirements of acute hemodialysis (HD) and death were analyzed.**

Results: **Twenty-two patients with H1N1 pneumonia were included: age: 52.91 ± 18.89 years; gender: males 11 (50%); chronic airway disease: 9 (41%); oncohematological disease: 8 (36.7%); cardiovascular disease 5 (22.7%); chronic renal insufficiency: 4 (18.2%); obesity 3 (13.6%); concomitant pregnancy: 2 (9.1%); diabetes mellitus: 2 (9.1%); previous influenza A vaccination: 9 (41%). All patients received oseltamivir within 48 hours of presumed diagnosis. Seventeen patients (77.3%) developed fever initially. Six patients (27.3%) required non-invasive ventilation assistance and 15 patients (68.2%) received invasive ventilatory support. Mean days on mechanical respiratory assistance: 11 ± 10.35. Arterial partial pressure of oxygen/fraction of inspired oxygen ratio: 140.11 ± 83.03 mmHg. Inotropic drugs were administered to 15 patients (68.2%). Fourteen patients (63.6%) developed AKI. Mean highest creatinine levels: 2.74 ± 2.83 mg/dl. Four patients (18.2%) needed renal replacement therapy with a mean duration of 15 ± 12 days. Six patients (42.9%) recovered renal function. AKI was associated with pregnancy, immunosuppression, high APACHE, SOFA and MURRAY scores, and less time on mechanical ventilation assistance, hemodynamical instability and thrombocytopenia. HD requirements were associated with elevated SOFA scores (12.25 ± 1.75 vs. 6.22 ± 0.8, p<0.05), elevated creatine phosphokinase (933 ± 436.6 vs. 189.9 ± 79.3 U/L, p<0.05) and alanine transferase levels (843.3 ± 778.8 vs. 85.33 ± 17.4 U/L, p<0.05). Twelve patients died (54.6%), 10 of whom had acute renal failure (83.3%) and 3 had been on acute HD (25%). Mortality was associated with higher APACHE, SOFA and Murray scores, a higher oseltamivir dose (253.1 ± 25.8 vs. 183.8 ± 27.6 mg, p<0.05), lower oxygen inspired fraction/alveolar pressure ratio (99.3 ± 12.2 vs. 196.3 ± 33.9 mmHg, p<0.01), thrombocytopenia (88966 ± 22977 vs. 141200 ± 17282 mm^3, p<0.05), hypoalbuminemia (1.82 ± 0.1 vs. 2.61 ± 0.2 g/dl, p<0.01), acute renal failure (10 vs. 4, p<0.05), oliguria (5 vs. 0, p<0.05) and lack of recovery of renal function (2 vs. 4, p<0.01). Three out of 4 (75%) of the hemodialyzed patients died.**

Conclusions: **In the critically ill due to H1N1 pneumonia, renal insufficiency was a frequent complication, demanding renal replacement therapy in 18% of cases. The need for HD was associated with an elevated risk of death. Mortality was mainly associated with multiple organ failure, oliguria, acute renal injury and a lack of recovery of renal function.**

Key words: *Acute kidney injury, H1N1, Hemodialysis, Influenza A, Pneumonia, Rhabdomyolisis*

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Summary

The recent worldwide outbreak of H1N1 influenza A infection transiently altered the management of the critically ill patient, with a high demand on intensive care utilities, including acute hemodialysis (HD) treatments. During a 2-month period we studied all H1N1 pneumonia cases admitted to the intensive care unit and subsequently focused on acute kidney injury (AKI) cases. Renal injury developed in 63.6% of patients, requiring dialysis in 18% of cases; main significant risk factors included non-hematological immunosuppression and high APACHE and SOFA scores. Mortality was associated with oligoanuria, acute renal injury, the need for HD and a lack of recovery of renal function. Rhabdomyolisis may play a role in renal dysfunction.

Introduction

In late March and early April 2009 an outbreak of H1N1 influenza A virus infection was detected in Mexico, rapidly spreading to other countries as a result of airline travel (1-3). On 11 June 2009, the World Health Organization raised its pandemic alert to the highest level, 6. This pandemia was caused by an H1N1 influenza A virus strain that represents a quadruple reassortment of two swine, one human and one avian strains of influenza (4, 5). As of 31 July 2009, over 162,000 laboratory-confirmed cases had been reported in over 160 countries (2). Nevertheless, it is believed that the true numbers of cases are many times higher than the confirmed ones (6).

Some typical clinical features of H1N1 infection are its easy airborne spreading and a dissimilar target age, with an apparent predilection of affecting young individuals, with an estimate age range between 5 and 59 years old in Mexico (7), and affecting very young and very old people in the United States, similar to the age distribution that is described with seasonal influenza (8). Common risk factors for H1N1 complications include chronic lung disease, immunosuppressive states, cardiac disease, pregnancy, diabetes and obesity (9). Both leukopenia and leukocytosis, elevated liver aminotransferases (ALT), elevated lactic dehydrogenase (LDH) and creatine phosphokinase (CK) have been described. However, renal insufficiency is rarely mentioned. Moreover, viral infection is rarely linked to acute renal failure in the general population, even in critically ill patients, unless unusual complications arise.

We decided to study retrospectively all the PCR-confirmed H1N1 pneumonia cases admitted to the intensive care units of two similar community hospitals between May and July 2009, when the infection rate apparently found its highest peak in Argentina, and we focused on those individuals who conse-

TABLE I
GENERAL PATIENTS CHARACTERISTICS

Variable	Mean ± SD or frequency	With acute kidney injury	Without acute kidney injury	P
Age (years)	52.91 ± 18.89	55.86 ± 20.76	47.75 ± 14.94	ns
Gender (males)	11 (50%)	5	6	ns
Chronic renal failure	4 (18.18%)	3	1	ns
Chronic lung disease	9 (40.91%)	6	3	ns
Chronic cardiac disease	5 (22.73%)	4	1	ns
Diabetes mellitus	2 (9.09%)	2	0	ns
Obesity	3 (13.64%)	1	2	ns
Pregnancy	2 (9.09%)	2	0	<0.05
Oncohematologic disease	8 (36.36%)	6	2	ns
Kidney transplant	1 (4.55%)	1	0	ns
Human immunodeficiency virus infection	2 (9.09%)	2	0	ns
Other immunosuppressions	6 (27.27%)	6	0	< 0.05
Previous Influenza vaccine	9 (40.91%)	6	3	ns

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quently developed AKI, the need for acute HD and assessed eventual risk factors of renal involvement and mortality.

Subjects and methods

Twenty-two critically compromised patients with H1N1 pneumonia were identified. Table I depicts patient characteristics. H1N1 infection was established with a nasopharyngeal swab with a synthetic tip or endotracheal aspirate as appropriate. Specimens were placed on ice and kept refrigerated until processed at the state health department laboratory. The test employed was reverse transcriptase-PCR for influenza A, B, and H1. All patients received oseltamivir empirically, adjusted to renal function and they continued on that therapy thereafter. H1N1 pneumonia was diagnosed on clinical, gasometric and imaging by chest X-rays and computed tomography scans. Considered variables included: APACHE (10), SOFA (11) and Murray (12) scores, fever, oseltamivir dose, requirements and period of ventilatory assistance, partial pressure of arterial oxygen to fraction of inspired oxygen ratio (PAFI), use of inotropics, serum creatinine, LDH, CK, ALT, albuminemia, leukocyte counts, platelet numbers and hemoglobin levels. AKI and the requirements of renal replacement therapy were defined according to RI-

TABLE II
CLINICAL AND LABORATORY DATA

Result	Mean ± SD or frequency	AKI (n=14)	Without AKI (n=8)	P
Apache score	22.09 ± 9.98	26.64 ± 2.51	14.2 ± 1.63	<0.01
Sofa score	7.32 ± 4.22	9.21 ± 1.01	4 ± 0.94	<0.01
Murray score	2.057 ± 1.45	2.46 ± 1.27	1.34 ± 1.54	<0.05
Fever at onset	17 (77.3%)	12 (85.71%)	5 (62.5%)	ns
Fever on admission	13 (59.1%)	10 (71.43%)	3 (37.5%)	ns
Oseltamivir dose (mg/day)	221.59 ± 93.2	241.07 ± 101.6	187.5 ± 69	ns
Non-invasive ventilatory assistance	6 (27.3%)	4 (28.57%)	2 (25%)	ns
Invasive ventilatory assistance	15 (68.2%)	12 (85.71%)	2 (25%)	<0.05
Days on ventilatory assistance	11.93 ± 10.35	8.5 ± 8.42	25.7 ± 2.52	<0.05
$PAFiO_2$ ratio	140.11 ± 83.03%	180.16 ± 120.23	121.62 ± 56.09	ns
Inotropic drugs used	15 (68.2%)	12 (85.71%)	3 (37.5%)	<0.05
LDH (U/L)	646.15 ± 526.12	534.4 ± 279.21	1018.67 ± 1019.54	ns
CK (U/L)	349.14 ± 491.21	475.78 ± 569.86	121.2 ± 183.45	ns
ALT (U/L)	223.13 ± 663.68	304.93 ± 831.48	80 ± 25.81	ns
Platelets (mm^3)	112709 ± 72852	91828 ± 69018	149250 ± 68393	<0.05
Highest leukocyte count (mm^3)	15525 ± 9786	13762.86 ± 9870.48	18608.75 ± 9448.9	ns
Lowest leukocyte count (mm^3)	5577 ± 3921	5254 ± 4662	6141 ± 2274	ns
Hemoglobin (g/dl)	8.72 ± 2.30	8.39 ± 2.41	9.31 ± 2.11	ns
Albumin (g/dl)	2.18 ± 0.63	1.95 ± 0.49	2.59 ± 0.68	ns

AKI = acute kidney injury.

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FLE criteria (13). Inotropic drugs employed included: norepinephrine (average dose: 0.08 µg/kg/min), dopamine (5.4 µg/kg/min) and dobutamine (6.2 µg/kg/min) in order to maintain a mean blood pressure capable of ensuring adequate tissue perfusion. Antibiotics were employed in different combinations in all patients and included clarithromycin, cefipime, metronidazol, itraconazole, vancomycin, levofloxacin, ceftriaxone, piperacillin-tazonam, trimetoprim-sulfametoxazole, colistin and ceftazidime, according to empirical approaches or bacteriologic findings. Each acute HD daily session was prescribed according to the clinical situation and mainly consisted of bicarbonate-based intermittent prolonged sessions using low-flux biocompatible membranes. Finally, the variables associated with AKI, the need for HD and mortality risk factors were identified and analyzed.

Results are expressed as mean ± standard deviation. According to the analyzed variable, chi^2 or the Student's t-test were employed. A value $p<0.05$ was considered to be significant. The STATA 8.0 Statistics/Data Analysis program was used (1984-2003 Stata Corporation ®, Texas USA). The Teaching and Research Committee of both hospitals approved the analysis of data.

Results

Tables I and II summarize the main clinical and laboratory data. AKI was diagnosed in 14 patients (Tabs. I-III). Significant differences between patients who developed AKI vs. those who did not included, respectively: pregnancy, 2 vs. 0, $p<0.05$; non-hematological immunosuppression, 6 vs. 0, $p<0.05$; APACHE score, 26.64 ± 2.51 vs. 14.2 ± 1.63, $p<0.01$; SOFA score, 9.21 ± 1.01 vs. 4±0.94, $p<0.01$; MURRAY score, 0.55 ± 0.34 vs. 1.34 ± 2.46, $p<0.05$; mechanical respiratory assistance, 12 vs. 2, $p<0.05$; days on

TABLE III
RENAL ASPECTS

Acute renal failure N=14	AKI with RRT N=4 (28.57%)	AKI without RRT N=10 (71.42%)	P
Sofa	12.25 ± 3.5	8 ± 3.26	<0.05
Rifle	Risk 0 Injury 0 Failure 4 (100%)	Risk 7 (70%) Injury 3 (30%) Failure 0	ns ns <0.01
Oliguria	2 (50%)	2 (20%)	ns
Days on hemodialysis	15 ± 12.02	NA	
Type of renal replacement therapy	Intermittent 1 Prolonged 3 Continuous 1	NA	
Recovery of renal function	1 (25%)	5 (50%)	ns
Deaths	3 (75%)	7 (70%)	ns
Highest creatinine level (mg/dl)	2.23 + 3.66	1.80 + 3.58	ns
Lowest creatinine level (mg/dl)	0.87 + 0.46	0.81 + 0.42	ns
Ck peak (u/l)	933 ± 436.56	189.91 ± 79.29	< 0.01
Alt (u/l)	843.25 ± 778.75	85.33 ± 17.39	<0.05

AKI = acute kidney injury; RRT = renal replacement therapy; ns = non-significant; NA = not applicable.

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mechanical ventilation, 8.5 vs. 25.66, p<0.05; lower platelet levels, 91828 ± 18446 vs. 149250 ± 24181, p<0.05; and use of inotropic drugs, 12 vs. 3, p<0.05. Table IV details the risk factors associated with mortality. Four patients required HD (Tabs. III and IV), 3 of whom died. Those patients who required renal replacement therapy showed the following significant differences compared to those who did not: higher SOFA scores, 12.25 ± 1.75 vs. 6.22 ± 0.84, p<0.05; CK levels 933 ± 436.56 vs. 189.91 ± 79.29 U/L, p<0.01; and ALT concentrations, 843.25 ± 778.75 vs. 85.33±17.39 U/L, p<0.05 (Tab. III).

Discussion

Our study shows that H1N1 pneumonia caused AKI in 63.6% of severely injured patients, and was associated with pregnancy, immunosuppression, multi-organ failure with inotropic requirements and thrombocytopenia, the latter finding presumably due to rhabdomyolysis and/or disseminated intravascular coagulation. A shorter period on mechanical ventilation assistance could be due to a more rapid and worse clinical evolution compared to the group without renal impairment. The requirements of renal replacement therapy were related to high SOFA scores, and elevated levels of ALT and CK, probably due to rhabdomyolysis. When HD was required, it presented a 75% of risk of death. Finally, mortality reached 54.6% and was associated with severe clinical compromise, hypoxemia, AKI, thrombocytopenia, hypoalbuminemia and a higher oseltamivir dose, albeit the drug was adjusted to renal function. This last observation could not be clearly explained. Although oseltamivir is mainly excreted by the kidneys, there is a general lack of experience with its management, probably contributing to renal damage. Once kidney compromise is established, the oseltamivir dose is not discontinued and maybe not as useful as in the first days of infection. Finally, multiple antibiotics were administered to our patients, and this certainly could have caused nephrotoxicity.

Acute renal failure and sepsis in the critically ill adult is rarely associated with viruses. Viral causes of intrinsic acute renal dysfunction include Hepatitis B and C, HIV, cytomegalovirus and parvovirus B19 in the setting of immunosuppression, and less commonly, Epstein Barr, measles, mumps, Coxsackie and Hantavirus (14-16).

Influenza A can cause serious and potentially fatal complications, including pneumonia, myocarditis, pericarditis and a variety of neurological disorders (17). Since most patients with influenza A virus infection have no serious complica-

TABLE IV
SIGNIFICANT RESULTS ASSOCIATED WITH MORTALITY

Variable	Survived	Deceased	P value
N	10	12	ns
Age	58.8 ± 17.69	48 ± 19.18	ns
APACHE score	16.6 ± 2.88	26.66 ± 2.45	<0.01
SOFA score	4.3 ± 1.02	9.83 ± 0.92	<0.01
Murray score	1 ± 0.37	2.94 ± 0.29	<0.01
Patients with AKI	4	10	<0.05
Oligoanuria (<400ml/day)	0	5	<0.05
Patients with RRT	1	3	ns
Renal function recovery	4	2	<0.01
Oseltamivir (mg/day)	183.75 ± 27.64	253.13 ± 25.75	<0.05
Non-invasive ventilatory assistance	6	0	<0.01
$PAFiO_2$ ratio	196.25 ± 33.83	99.27 ± 12.23	<0.01
Platelets (mm^3)	141200 ± 17282.03	88966.67 ± 22977.91	<0.05
Albumin (g/dl)	2.61 ± 0.19	1.82 ± 0.12	<0.01
Creatinine peak (mg/dl)	1.50 ±_2.83	1.74 ±_3.08	ns
CK peak (U/L)	157.71 ± 155	540.57 ± 642	ns
ALT peak (U/L)	68.9 ± 33.2	351.67 ± 894.62	ns

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tions and do not need hospitalization, the actual incidence of renal injury in unknown. However, influenza A virus has rarely been implicated as a cause of acute renal failure in severely compromised patients and the literature is limited in this respect (18-21). In this setting, rhabdomyolysis appears to be the main pathophysiologic mechanism involved (15, 19, 22), albeit other renal complications, particularly in critically ill patients include thrombotic microangiopathy, disseminated intravascular coagulation and Goodpasture's syndrome (20, 23-25). Recently, it has been reported that 12 patients with avian influenza virus (H5N1) infection and severe disease presented a high rate of complications, including 3 cases of acute renal failure due to rhabdomyolysis (21). In a retrospective pediatric review on renal involvement in children with influenza A infection, acute renal involvement was reported in 24.4% of cases, five of whom developed acute renal failure associated with multiple organ dysfunction in 3 cases, rhabdomyolysis in 1 case and hemolytic-uremic syndrome in the remaining one. Hemodynamic instability, thrombocytopenia, rhabdomyolysis, elevated ALTs and LDH concentrations on admission were more common in patients with renal involvement. The mortality rate was significantly higher in patients with renal dysfunction (20).

Of note, and in agreement with our findings, CK levels can vary substantially, and even slightly elevated concentrations of the enzyme can be involved in muscle compromise. Unfortunately we lack plasmatic or urinary measurements of myoglobin to strengthen our hypothesis, but elevated CK levels coupled with concomitant elevations of intracellular enzymes (ALT and LDH) suggest a strong diagnosis of rhabdomyolisis (15). In a review by Singh et al concerning infectious causes of rhabdomyolysis, influenza is the leading reported viral cause, followed by HIV and enteroviruses. As mentioned previously, and lacking myoglobin measurements, the authors assumed rhabdomyolisis was caused by viruses, and CK levels varied between 203 and 303,200 U/L. CK levels were independently linked to renal compromise, 44% of patients presented with acute renal failure and the mortality rate was 12%. Interestingly, when compared to the other causes of viral rhabdomyolysis, despite the lowest CK levels, influenza was one of the most important causes of acute renal failure (15). To date, albeit that many hypotheses exist, the mechanisms of muscle compromise due to influenza remain unknown (15). Finally, in another review by Tanaka et al, 15/42 patients (36%) with virus-induced rhabdomyolysis had acute renal failure, again diagnosed by elevated CK levels. It is interesting that although influenza virus accounted for only 33% of rhabdomyolysis cases, 53% of patients with renal failure had this infection. In addition, the conditions of 57% of patients with influenza virus infection progressed to renal failure; these patients had CK concentrations widely ranging from 261 U/L to >50,000 U/L. However, most of these patients (11/14) had CK levels of <20,000 U/L (26).

The renal dysfunction associated with rhabmomyolysis could be due to several factors: myoglobin as a direct nephrotoxin (27, 28), which, in combination with hypovolemia and cortical ischemia, leads to tubular obstruction and acute renal failure. In turn, 4 potential pathogenic mechanisms have been postulated to explain the renal injury caused by influenza A: rhabdomyolysis, renal hypoperfusion, disseminated intravascular coagulation, and direct viral injury to the kidney, although the latter has not yet been proved (20). Our patients displayed hemodynamic instability in many cases due to sepsis and septic shock. This situation, coupled with the inherent nephrotoxic effects of the antibiotics usually employed in this setting, certainly could have added morbidity and mortality to the clinical picture.

According to our short observation, we believe that in critically affected patients with H1N1 pneumonia, septic shock is an unusual but serious complication. In addition to the usual and general intensive support given to this population, measures must be undertaken in order to avoid renal hypoperfusion, and the physician must be aware from the beginning that covert rhabdomyolysis may lead to renal failure, and is independent of the augmented degree of CK levels, and measures to deal with this situation must be promptly undertaken, because once occurring it will certainly add a substantial risk of death to affected patients.

H1N1 is a recent unexpected disease whose face is just gradually being shown to us. We believe a prospective recollection of all cases of H1N1 must be undertaken, and a multicenter retrospective analysis with a larger number of cases will be useful, as multivariate analysis is needed to analyze and identify independent risk factors associated with mortality and AKI. This is one of the limitations of this work.

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