case report

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Influenza A(H1N1) infection and severe cardiac dysfunction in adults: A case series

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Influenza A(H1N1) Infektion und schwere kardiale Dysfunktion bei Erwachsenen: Eine Fallserie

Zusammenfassung. *Hintergrund:* Während die virale Myokarditis und das Herzversagen anerkannte und gefürchtete Komplikationen einer saisonalen Influenza A Infektion sind, liegen bislang nur wenig Informationen über ein durch das 2009 Influenza A(H1N1) Virus induziertes Herzversagen vor.

Methoden und Hauptergebnisse: Diese Fallsammlung fasst den Krankheitsverlauf von vier Patienten mit 2009 Influenza A(H1N1) Infektion zusammen, welche an unserer Klinik im Zeitraum von November 2009 bis September 2010 behandelt wurden. Alle Patienten präsentierten sich mit einer schweren kardialen Funktionsstörung (akutes Herzversagen, kardiogener Schock oder Herzkreislaufstillstand im Rahmen eines Kammerflimmerns) als das führende Symptom einer Influenza A(H1N1) Infektion. Zwei Patienten waren mit hoher Wahrscheinlichkeit kardial vorerkrankt, und drei benötigten eine Katecholamintherapie, um die hämodynamische Funktion zu stabilisieren. Mit Ausnahme eines Patienten der vor der Diagnosestellung der Influenza A(H1N1) Infektion verstarb, wurden alle Patienten mit einer antiviralen Therapie mit Oseltamivir und supportiver Intensivtherapie behandelt. Ein Acute Respiratory Distress Syndrom infolge der Influenza A(H1N1) Infektion trat bei einem Patienten auf. Die Herzfunktion normalisierte sich bei zwei Patienten und war bei einem Patienten noch bei Krankenhausentlassung eingeschränkt.

Schlussfolgerung: Eine Influenza A(H1N1) Infektion kann mit einer schweren kardialen Funktionseinschränkung assoziiert sein. Diese kann sich sogar als führendes klinisches Symptom darstellen. Während einer Influenza Pandemie kann eine genaue Anamneseerhebung Grippeähnliche Symptome hervorbringen und sollte auch bei kritisch kranken Patienten mit akutem Herzversagen eine Diagnostik auf H1N1 Infektion veranlassen.

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Summary. *Background:* While viral myocarditis and heart failure are recognized and feared complications of seasonal influenza A infection, only limited information is available for 2009 influenza A(H1N1)-induced heart failure.

Methods and main findings: This case series summarizes the disease course of four patients with 2009 influenza A(H1N1) infection who were treated at our institution from November 2009 until September 2010. All patients presented with severe cardiac dysfunction (acute heart failure, cardiogenic shock or cardiac arrest due to ventricular fibrillation) as the leading symptom of influenza A(H1N1) infection. Two patients most likely had pre-existent cardiac pathologies, and three required catecholamine therapy to maintain hemodynamic function. Except for one patient who died before influenza A(H1N1) infection had been diagnosed, all patients received antiviral therapy with oseltamivir and supportive critical care. Acute respiratory distress syndrome due to influenza A(H1N1) infection developed in one patient. Heart function normalized in two of the three surviving patients but remained impaired in the other one at hospital discharge.

Conclusions: Influenza A(H1N1) infection may be associated with severe cardiac dysfunction which can even be the leading clinical symptom at presentation. During an influenza pandemic, a thorough history may reveal flu-like symptoms and should indicate testing for H1N1 infection also in critically ill patients with acute heart failure.

Key words: Influenza, H1N1, acute heart failure, cardiac arrest, cardiogenic shock.

Introduction

During 2009, a novel influenza A virus of swine origin (H1N1) emerged to cause human infection [1–3]. The virus rapidly spread worldwide and caused a serious influenza pandemic throughout the Southern hemisphere in 2009 [4]. In fall of 2009, its activity increased again in the Northern hemisphere [5]. As of August 1, 2010, at least 18,449 deaths due to laboratory confirmed infections with the H1N1 virus were reported to the World Health Organization from 214 countries [5].

Although viral myocarditis and heart failure are well-recognized and feared complications of seasonal influenza A infection [6], only limited information on H1N1-induced heart failure has been reported so far [7–10]. This case series summarizes the disease course of four patients with 2009 influenza A(H1N1) infection who were treated at our institution from November 2009 until September 2010. All patients presented with acute heart failure, cardiogenic shock or cardiac arrest as the leading symptom. The institutional review board of the Inselspital and Medical University of Bern gave approval for this research.

Case presentations

Case 1

A 55-year-old Caucasian female was admitted because of ventricular tachycardia after complaining about flu-like symptoms and palpitations. She had experienced a self-limited episode of palpitations one month earlier. Echocardiography revealed a dilated left ventricle with anterior wall akinesia and reduced ejection fraction (10–15%). Since ventricular tachycardia persisted despite pharmacologic and electric cardioversion attempts, the patient was transferred to this hospital. Coronary angiography showed that chronic occlusion of the left anterior descending coronary artery considered inappropriate for revascularization. An intra-aortic balloon pump was inserted, and the patient was intubated. On admission to the intensive care unit (ICU), she presented with cardiogenic shock (arterial blood pressure, 75/58/46 mmHg; cardiac output, 2.3 L/min), pulmonary edema (PaO_2/FiO_2 quotient, 145; pulmonary arterial occlusion pressure, 24 mmHg), and persistent ventricular tachycardia. Three episodes of ventricular fibrillation were terminated by defibrillation. After repeated administration of amiodarone and lidocaine, and institution of a glucose-insulin-potassium infusion, ventricular tachycardia was electrically converted into sinus rhythm. The patient required catecholamines (dobutamine, epinephrine) and milrinone. Laboratory investigations for possible high urgency heart transplantation were ordered, and implantation of a left ventricular assist device was discussed. Additionally, a nasopharyngeal swab for influenza H1N1 was obtained [11]. By ICU day 2, hemodynamic function slightly improved and nitroprusside was started. After receipt of the positive H1N1 virus test results, she was started on oseltamivir (2×150 mg/d). During the following days, cardiogenic shock resolved, and the patient was weaned off the mechanical ventilator. Six days after admission, she was transferred to the cardiology ward. Oseltamivir treatment was continued for ten days. At hospital discharge, left ventricular ejection fraction remained low at 15–20%.

Case 2

A 59-year-old Caucasian male presented to a district hospital with dyspnea and flu-like symptoms. Echocardiography showed dilatation of the right ventricle, interventricular septal bulging, and decreased left ventricular ejection fraction (15–20%). After an epinephrine infusion had been started because of arterial hypotension (62/45/35 mmHg), the patient was transferred to this ICU. On admission, he remained hypotensive (mean arterial pressure, 35–45 mmHg) with lactic acidosis (arterial lactate, 22 mmol/L; arterial pH, 6.8) and required repetitive epinephrine bolus injections, dobutamine, endotracheal intubation, and buffering. Pulmonary gas exchange was not compromised (PaO_2/FiO_2 quotient 400). As the right ventricle remained dilated in echocardiography and cardiac enzymes were only mildly elevated with a S_IQ_{III} type on the electrocardiogram, pulmonary embolism was suspected. Intravenous thrombolysis with 100 mg alteplase (Actilyse®; Boehringer Ingelheim, Basel, Switzerland) was performed. Nevertheless, hemodynamic function continued to deteriorate, and epinephrine requirements increased. Six hours following admission, the patient died from refractory cardiogenic shock. The post-mortem examination found a dilated and hypertrophic heart (610 g) with amyloidosis and moderate coronary sclerosis but no fresh thrombus. Signs of chronic pulmonary arterial hypertension, pulmonary edema, and tracheitis but no pulmonary embolus was detected. A nasopharyngeal swab collected on ICU admission turned out positive for H1N1.

Case 3

After five days of flu-like symptoms, a 43-year-old female returned to work where ventricular fibrillation occurred. Following four cycles of cardiopulmonary resuscitation by the ambulance service, return of spontaneous circulation was achieved. On hospital admission, blood pressure was stable (100/70/52 mmHg) and echocardiography revealed preserved biventricular pump function without regional wall motion abnormalities or pericardial effusion. No intracranial pathology or pulmonary embolism was detected on computed tomography. Shortly after ICU admission, the patient experienced another three episodes of ventricular fibrillation requiring defibrillation. Therapeutic hypothermia (33–34°C) was initiated for 12 hours. Following rewarming, a coronary angiography showed no signs of coronary artery disease. The nasopharyngeal swab taken at ICU admission was positive for H1N1. Oseltamivir (2×150 mg/d) was started. There were no signs of impaired pulmonary function (PaO_2/FiO_2 quotient, 450) but mild bilateral infiltrates were seen on chest X-ray. After withdrawal of sedation, the patient developed focal seizures. An electroencephalogram showed status epilepticus which was treated with levetiracetam (2×1 g/d), propofol, and eventually additional clonazepam and valproic acid. While cardiovascular function remained stable and no further arrhythmias occurred, she remained unconscious (Glasgow Coma Scale 6) despite cessation of epileptic activity. After tracheostomy and weaning from the mechanical ventilator, the patient was discharged to a neurologic rehabilitation unit with persistent neurologic impairment on ICU day 14.

Case 4

Following an eight days history of upper respiratory tract infection with five days of antibiotic treatment (erythromycin and amoxicillin), a 29-year-old Indian female was trans-

Table 1. Patient characteristics and clinical symptoms

	Case 1	Case 2	Case 3	Case 4
Age (years)	55	59	43	29
Gender	female	male	female	female
Ethnic group	Caucasian	Caucasian	Caucasian	Indian
Premorbidities	bronchial asthma, tobacco abuse (25 py)	multiple myeloma, retinitis pigmentosa, arterial hypertension, atrial fibrillation	hypothyroidism	epilepsy, diabetes mellitus type I
Days of Flu-like symptoms	2	3	5	8
Flu-like symptoms	fever, headache, myalgia, dyspnea	fever, cough, fatigue, headache	fever, chills, cough	fever, cough, fatigue, myalgia
First white blood cell count (G/L)	12.2	5.6	8.6	7.7
First C-reactive protein (mg/L)	126	32	<3	35
max. Creatinkinase (IU/L)	977	1286	931	757
max. Creatinkinase MB (IU/L)	6.3	138.9	31	3.8
max.Troponin T (mg/L)	0.139	3.06	0.24	0.052
Initial presentation at admission	ventricular tachycardia, cardiogenic shock	biventricular heart failure	cardiac arrest	acute left heart failure
SAPS II (pts)	52	62	58	32
max. SOFA Score (pts)	9	11	8	181
Length of ICU stay (days)	6	1	14	28
ICU mortality	alive	dead	alive	alive

py pack years; *SAPS* Simplified Acute Physiology Score; *SOFA* Sequential Organ Failure Assessment; *ICU* intensive care unit.

ferred to our ICU from a regional hospital center with acute respiratory and heart failure. Initial echocardiography revealed impaired left ventricular function (left ventricular ejection fraction 40%) without regional abnormalities. At ICU admission, she presented with acute left heart failure (cardiac output, 2.4 L/min/m^2; pulmonary capillary occlusion pressure, 21 mmHg; mixed venous oxygen saturation, 47%) and acute respiratory failure (PaO_2/FiO_2 quotient, 150). Her laboratory studies were notable for elevated plasma troponin T (0.052 µg/L) and creatinkinase levels (757 IU/L) (Table 1). The patient was started on dobutamine and subsequently nitroprusside infusion. A computertomography scan of the chest displayed dense bilateral perihilar infiltrates. Empiric antibiotic therapy with ceftriaxone, levofloxacin, and vancomycin was installed. A nasal swab taken on ICU admission proved positive for influenza A(H1N1). Treatment with oseltamivir (2×150 mg/d) was initiated. Her subsequent course was procrastinated as she developed severe acute respiratory distress secondary to influenza A(H1N1) infection. Hemodynamic support was required until ICU day 8 after which cardiac function had normalized. The patient could only be weaned off the ventilator slowly and underwent tracheotomy on ICU day 14. Twenty-eight days after ICU admission, the patient was discharged to a pulmonary ward with normalized heart function but impaired respiratory capacity.

Discussion

In all presented patients with proven influenza A(H1N1) infection, acute heart failure, cardiogenic shock or cardiac arrest was the cause for hospital or ICU admission. It is impossible to differentiate from the data of this case series whether acute heart failure represented H1N1-induced myocarditis or secondary myocardial dysfunction [12]. Thus, also pre-existing cardiac disease may predispose to influenza A(H1N1) infection. Although the clinical course of patients 3 and 4 closely resembled viral myocarditis, this clinical suspicion could not be ascertained as myocardial biopsy was refrained from due to lacking therapeutic consequences. Similarly, it remains unclear to which extent H1N1 infection contributed to acute deterioration of pump function in patients 1 and 2.

Given that all patients had a history of flu-like symptoms, it is unlikely that they were asymptomatic H1N1 carriers independently experiencing acute heart failure. Nonetheless, their initial presentation of acute heart failure was severe in all patients overriding characteristic signs of influenza A(H1N1). Only thorough examination of the patient's history allowed establishment of the diagnosis of H1N1 infection. Although it is unclear to what extent antiviral therapy contributed to the improvement of heart function in patients 1, 3 and 4, it is possible that treatment of H1N1 infection was beneficial for the recovery of heart function.

So far, emerging but limited data on H1N1-associated cardiac dysfunction is available. The major case series of 2009 influenza A(H1N1) infections [1, 4, 7, 9 13–17] did not report any patient with acute heart failure as the leading clinical symptom. Just recently, Martin et al. have retrospectively identified reversible cardiac dysfunction in six out of 123 cases (4.9%) with influenza A(H1N1) infection

[10]. However, none of these cases initially presented with symptoms of acute heart failure. One patient with fulminant myocarditis was excluded from the ANZECMO study but was not reported in more detail [18]. Two patients in the English cohort [9] had cardiac causes of death possibly related to influenza A(H1N1) infection. A case of biopsy proven myocarditis which was associated with acute H1N1 infection was published in the Finnish literature [8]. Fulminant myocarditis has been reported in children infected with the pandemic influenza A(H1N1) virus [19]. In our own experience, all other cases of 2009 influenza A(H1N1) who had so far been admitted to our ICU, presented with flu-like symptoms and signs of respiratory tract infection (8 cases) except for one case of acute brain trauma where test results coincidentally revealed asymptomatic carrier status.

Considering that the H1N1 virus strain is a subtype of the influenza type A viral group [2], which was repeatedly associated with cardiotoxicity [6], the lack of reports of heart failure in patients with 2009 influenza A(H1N1) is surprising. This finding may reflect a certain publication bias. On the other hand, it could be speculated that influenza A(H1N1) testing has so far been performed only sporadically in patients admitted because of cardiogenic shock or cardiac arrest. In contrast to acute heart failure as the leading symptom of H1N1 infection, firm evidence exists that patients with chronic cardiovascular diseases are at increased risk of acquiring H1N1 infection and thus cardiovascular disease could be considered as a pre-existing condition [13–17, 20]. Accordingly, it must be assumed that patients 1 and 2 had a chronic cardiac pathology. Although not diagnosed beforehand, the post-mortem examination revealed cardiac amyloidosis and hypertrophy with pulmonary arterial hypertension in patient 2 suggesting that his cardiomyopathy was pre-existent. Similarly, the history of palpitations earlier before admission in patient 1 together with chronic occlusion of the left anterior descending coronary artery indicate that she suffered from chronic coronary artery disease.

Although this case series presents the individual disease course of four patients only and can establish neither the actual incidence of heart failure in 2009 influenza A(H1N1) infection nor a causative relationship between H1N1 infection and heart failure, we believe that relevant clinical conclusions can be drawn form this report: First, in critically ill patients presenting with acute heart failure or other critical illness a thorough history may reveal flu-like symptoms and should indicate testing for H1N1 infection. Second, infection with the 2009 influenza A(H1N1) virus may be associated with acute heart failure and cardiac arrest as the leading clinical symptom.

Conflict of interest

No author has a conflict of interest in regard to drugs or techniques discussed in this manuscript.

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