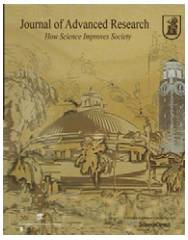
Journal of Advanced Research (2011) 2, 191–194

Cairo University

Journal of Advanced Research



CASE REPORT

Fatal acute myocarditis and fulminant hepatic failure in an infant with pandemic human influenza A, H1N1 (2009) virus infection

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Received 4 September 2010; revised 21 December 2010; accepted 7 January 2011
Available online 22 February 2011

KEYWORDS

Influenza (H1N1) infection;
Acute myocarditis;
Fulminant hepatic failure

Abstract We report the clinical presentation of a 10 month-old infant who succumbed with acute myocarditis and fulminant hepatic failure associated with a virologically confirmed human influenza A, H1N1 (2009) virus infection. To date, this is the first pediatric patient presenting with this fatal combination of complications during the current H1N1 pandemic. Therefore, we recommend meticulous assessment and follow up of the cardiac status, liver enzymes and coagulation profile in all pediatric patients with severe H1N1 influenza infection.

Introduction

The human influenza A, H1N1 (2009) virus pandemic has seriously hit numerous countries all over the world, including Egypt. Cases started to be reported in Egypt in June 2009, peaked in December 2009 and started to decline by April 2010. As of September 2nd, 2010, the total number of confirmed cases in Egypt was 16,373 (including 5675 school children) with 281 deaths [1]. The total population of Egypt is almost 85,800,000.

The multi-organ distribution of H1N1 virus is unknown and the ability to spread to multiple organs may be a more common property of influenza viruses in mammalian hosts than previously believed [2]. Studies in mouse models suggest a more common multiple organ localization than previously believed, including the lung, heart, thymus, liver and spleen [2]. Researchers from Rady Children's Hospital in San Diego, CA, United States, have recently published the first known report of acute myocarditis in a pediatric population associated with the present pandemic H1N1 influenza A virus infection [3]. Researchers from the Universitat de Barcelona, Barcelona, Spain have published novel influenza A (H1N1) encephalitis in a 3-month-old infant [4].

Case report

Our case was a 10 month old male infant, a second sib of non-consanguineous healthy Egyptian parents, who was admitted

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2090-1232

Peer review under responsibility of Cairo University.
doi:10.1016/j.jare.2011.01.003

Production and hosting by Elsevier

to Cairo University Children's Hospital (Cairo, Egypt) in a general pediatric ward, on the 25th December, with high fever reaching up to 39 °C, cough and grade III respiratory distress of 3 day-duration.

Two previous hospital admissions with respiratory distress at the age of 3 and 5 months at a local hospital outside Cairo were diagnosed as bronchopneumonia. During the second admission echocardiography revealed a previously undiagnosed moderate-sized patent ductus arteriosus (PDA), 0.4 cm pulmonary end with left to right shunt, maximum pressure gradient across 55–60 mmHg, pulmonary artery systolic pressure 35 mmHg and fractional shortening (FS) 40% (Fig. 1). Accordingly, he was commenced on oral Frusemide and Captopril; and surgical closure of the ductus was contemplated.

On admission to our hospital, the infant was diagnosed as having bronchopneumonia with heart failure attributed to the PDA. He was started on intravenous (IV) antibiotics (Ampicillin/Sulbactam plus Cefotaxime), IV Frusemide and oral Captopril and after 48 h, he improved clinically with decreased respiratory distress and fever. However, 5 days later, he spiked fever again up to 40 °C and had an attack of hematemesis followed by drowsiness, cyanosis, hypotension and severe bronchospasm. An endotracheal tube was urgently placed, and he was rushed to the pediatric intensive care unit (PICU).

On PICU admission, the infant was tachypneic, stuporous, with spontaneous eye opening and flexion withdrawal to pain. There was a picture of bronchopneumonia suggested by chest examination revealing bilateral diminished air entry with extensive fine crepitations and wheezes and confirmed by chest X-ray revealing picture of bilateral bronchopneumonia and cardiomegaly (Fig. 2). Moreover, he had a picture of myocardial decompensation suggested by severe tachycardia, hypotension and an enlarged tender liver. Liver insult was also suspected as the patient was icteric with bleeding tendency (hematemesis and puncture sites). Cranial ultra-sonographic scan was normal, whereas an abdominal scan revealed moderate hepatomegaly with a homogenous liver echo pattern, markedly congested hepatic veins and a moderate amount of clear, free ascitic fluid.

He was put on full mechanical ventilation and was started on inotropes (Dopamine 8 mcg/kg/min and Dobutamine

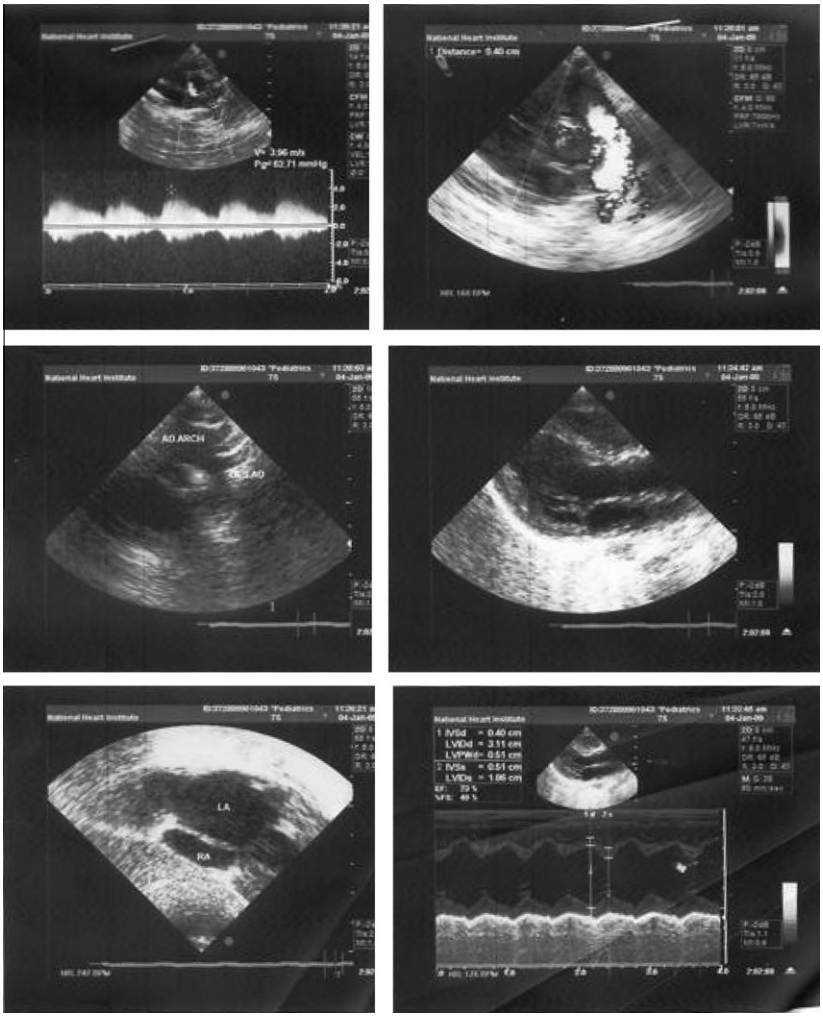

Fig. 1 Eechocardiography revealing a previously undiagnosed moderate-sized patent ductus arteriosus (PDA), 0.4 cm pulmonary end with left to right shunt, maximum pressure gradient across 55–60 mmHg, pulmonary artery systolic pressure 35 mmHg and fractional shortening (FS) 40%.

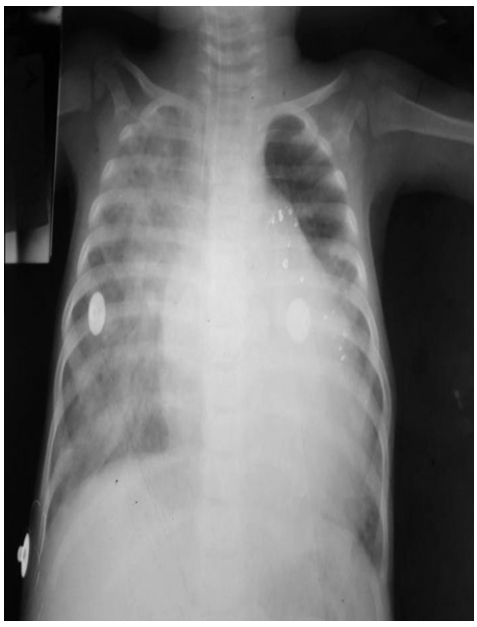

Fig. 2 Plain chest X-ray revealing a picture of bilateral bronchopneumonia and cardiac enlargement.

15 mcg/kg/min). In the PICU, the patient had a second attack of hematemesis and developed poor peripheral perfusion. Stomach wash with cold saline, vitamin K, H2 blocker (Zantac) and proton-pump inhibitor (Lozec) were added. Repeated plasma and blood transfusions were received with correction of the coagulopathy and stoppage of the hematemesis. IV Amikacin, oral Diflucan and inhaled Gentamicin were also added.

Laboratory investigations revealed markedly elevated liver enzymes [aspartate amino-transferase (AST) and alanine amino-transferase (ALT)], low serum albumin and prolonged international normalized ratio (INR) as seen in Table 1. Hepatitis A and B virus serological markers were negative. Blood ammonia was modestly elevated. IV vitamin K_1, oral lactulose, oral Neomycin and repeated enemas were added. When those laboratory findings and this clinical picture were associated with a negative C-reactive protein, it suggested a viral infection. A bedside echocardiographic examination in the PICU was compatible with a ''viral myocarditis'' with a very poor myocardial contractility and FS of 19% and confirmed the presence of a hemodynamically significant PDA of 5.5 mm diameter. Cardiac Troponin I and T were normal while MB fraction of creatine phosphokinase (CPK-MB) was elevated, possible due to the 2–3 h lag for Troponins to start serum elevations after CPK-MB starts its elevation. Therefore, the patient received intravenous immunoglobulins 5 g on the first day (700 mg/kg) due to availability in the emergency pharmacy, to be completed over another 2 days. But, with partial improvement noticed, another 2 days were added. The pandemic H1N1 influenza A virus was then suspected. The infant was started on Oseltamavir (2 mg/kg body weight every 12 h) on the second day of PICU admission. As practiced all over Egypt (http://www.mohp.gov.eg/swine_flu/news_details.aspx?id = 76&p = 0), a nasal swab for human influenza A, H1N1 (2009) virus was sent to the Egyptian Ministry of Health and Population Central Laboratories and real time reverse transcription polymerase chain reaction (RT-PCR) was positive for the virus. Sputum cultures revealed inhibited growth of normal bacterial flora and blood cultures showed no growth of aerobic or anaerobic bacteria.

The patient improved clinically after commencing Oseltamavir therapy manifested by improved conscious level, cardiac and chest conditions. This was noticed by better response to the inotropes in the form of maintained average blood pressure and peripheral perfusion, and better arterial blood gases with tendency to decrease the ventilatory settings. Biochemically, AST, ALT and INR decreased. It was then decided to maintain him for 10 days on Oseltamavir.

On day eight of Oseltamavir therapy, the patient deteriorated with severe hypoxemia due to bronchospasm necessitating increased ventilatory settings. He developed bilious vomiting, repeated attacks of convulsions and massive pulmonary hemorrhage. AST and ALT resurged and serum bilirubin increased. Renal functions also showed an acute kidney injury. Antibiotics were changed to Imepinem and Metronidazole in a trial to be more aggressively covering the possible nosocomial infections acquired in the PICU. He developed cardio-respiratory arrest with no response to resuscitation and died on the 10th day of PICU admission.

Discussion

It is now clear that, most unusually, healthy children and young adults are disproportionately affected among those with severe respiratory disease without underlying conditions due to H1N1 2009 influenza virus infection [5]. Children with an underlying co-morbid disease (such as big PDA in our case) represent a particular risk group when they contract H1N1 virus infection. Pandemic H1N1 2009 influenza has been reported to be associated with pediatric death rates 10 times the rates for seasonal influenza in previous years and most deaths were caused by refractory hypoxemia in infants less than 1 year of age [6]. Our patient was carefully maintained during his PICU admission on normal or near normal pO_2. The presence of a PDA in our case was an added risk factor. The initial improvement in a general ward might have given a false impression of starting cure until H1N1 infection was well advanced. Our infant was transferred to the PICU with multiple complications and when Oseltamavir therapy was commenced, it was probably late in the course of H1N1 infection. A secondary bacterial infection may also explain the deterioration that occurred, but since he was on antibiotics blood culture was not beneficial. Because of the very bad general condition of our patient and the instability of his condition, we were not able to do any invasive procedures such as liver or endomyocardial biopsies. To the best of our knowledge, our case is the first pediatric H1N1 influenza infection that presented with a fatal combination of the recently reported myocarditis [3] and the un-reported fulminant hepatic failure. Therefore, during the current H1N1 pandemic, we recommend meticulous assessment and follow up of the cardiac status, liver enzymes and coagulation profile in pediatric cases with severe H1N1 influenza infection.

Table 1 Laboratory investigations arranged according to hospital days.

Parameters	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12
WBC (10^3/mm^3)		23	9.8	10.3	15.7	12.8		8.6		15.7		
RBC (10^6/mm^3)		3.2	3.66	3.56	4.73	3.9		2.7		4.29		
HGB (g/dl)		6.6	7.4	6.9	11.2	9.3		5.4		11.4		
HCT (%)		19.7	23.4	24.8	34.9	29.5		18.6		32.5		
MCV (μm^3)		60.7	63.8	69.7	73.8	75.4		69		75.7		
MCH (pg)		20.3	20.1	19.4	23.7	23.8		19.8		26.6		
MCHC (g/dl)		33.5	31.5	27.8	32.1	31.5		28.8		35.1		
PLT (10^3/mm^3)		259	229	144	116	50		115		91		
B (%)			0									
E (%)			2									
ST (%)			3									
SEG (%)			60									
LYMPH (%)			30									
M (%)			5									
ESR = 1st hour			25									
ESR = 2nd hour			45									
TBIL (mg/dl)			1.2							5.66		7.4
DBIL (mg/dl)			0.9							3.79		4.4
AST (U/l)			4052	699	1029	232	333			449	365	425
ALT (U/l)			1253	1306	1055	130	200			359	325	268
ALB (g/dl)			2.9		3.0	2.7	3.3			2.3	2.7	3.2
TP (g/dl)						6.2	5.8			6		
BUN (mg/dl)			48	39	36	34	39		98.2	117	110	128
CRE (mg/dl)			0.7	0.9	0.8	0.8	0.4		1.4	1.1	1.1	1.1
CHOL (mg/dl)			173		164							
NA (mmol/l)			148	147	148.6	146	138		144	136.7	140	146
K (mmol/l)			2.8	2.5	3.18	3.38			3.8	4.8	5.34	4.15
PHOS (mg/dl)										3.9		3.8
CA (mg/dl)						8.8				9.9		9.3
ALP (U/l)										59		
GLU (mg/dl)			179		128					112	94	
GGT (U/l)				55	59							
PT (s)	29.6	21.2	16.5									
PTT (s)	63	30.9	24.7									
PC (%)	25.1	44	65									
INR (%)	2.85	1.87	1.36									
CRP			−ve			−ve				−ve		
pH	7.15	7.4				7.6				7.34		
p_{CO_2}	56	43				37				51		
p_{O_2}	165	67				44				38		
HCO_3	19.5	32.2				38				28.2		

Key of abbreviations by order: WBC, white blood cell; RBC, red blood cell; HGB, hemoglobin; HCT, hematocrit; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; PLT, platelets; B, basophils; E, eosinophils; ST, staff; SEG, segmented; LYMPH, lymphocytes; M, monocytes; ESR, erythrocyte sedimentation rate; TBIL, total bilirubin; DBIL, direct bilirubin; AST, aspartate amino-transferase; ALT, alanine amino-transferase; ALB, albumin; TP, total protein; BUN, blood urea nitrogen; CRE, creatinine; CHOL, cholesterol; NA, sodium; K, potassium; PHOS, phosphorus; CA, calcium; ALP, alkaline phosphatase; GLU, glucose; GGT, gama glutamyl transferase; PT, prothrombin time; PTT, partial thromboplastin time; PC, prothrombin concentration; INR, international normalized ratio; CRP, c-reactive protein.
Day 1: 31/12/2009; Day 12: 11/1/2010.

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