H1N1 Pandemic – One Year Follow up Study

Abhijit Biswas[1*], Faisal Alam[2], Karen Hartery[3], Aidand O. Brien[3], Saad Mahdy[4], Phillip Hodnett[5], James O'Driscoll[4] and Catherine Motherway[4]

[1]*Clinical Fellow, Regional Anaesthesia, Toronto Western Hospital, Canada.*
[2]*Psychiatry, University College Hospital, Galway, Ireland.*
[3]*Respiratory Medicine, Mid Western Regional Hospital, Limerick, Ireland.*
[4]*Anaesthesia and Intensive Care, Mid Western Regional Hospital, Limerick, Ireland.*
[5]*Department of Radiology, Mid Western Regional Hospital, Limerick, Ireland.*

Authors' contributions

Short Research Article

ABSTRACT

Objective: We performed a one year follow up case series study to evaluate any residual systemic diseases in the patients who presented to our intensive care unit with H1N1pdm09 infection during the 2010/2011 flu epidemic. Twelve patients were admitted with H1N1pdm09 infection over a period of two months. Most of them had multi organ failure and needed various supports. All needed respiratory support varying from, non invasive ventilation, conventional ventilation and high frequency oscillation with some requiring extracorporeal support. Six patients suffered acute renal failure due to the infection and received renal replacement therapy.
Aim: This is a one year follow up case series study to evaluate any impairment in respiratory, cardiac, renal and neurocognitive function in this cohort of patients, who had suffered and were treated for H1N1 infection.

_____

Corresponding author: Email: avijitbsws@yahoo.com;

Study Design: Case Series study.
Methods: We assessed seven patients, one year after they had suffered from H1N1pdm09 infection. They were evaluated for pulmonary, cardiac, renal and neurocognitive function in our clinic. Rest of the five patients were interviewed over phone.
Results: Three of the seven patients had poor pulmonary function, indicating significant parenchymal lung injury. Two had moderate to severe restrictive lung disease. Few patients reported a significant impaired quality of life and cognitive impairment. Five patients had impaired phonological fluency, which could be due to hypoxic brain injury, post H1N1pdm09 ARDS. One of the patients, who had suffered acute renal failure, still had renal impairment.
Conclusion: Though all of these patients had survived and were discharged home, a number of them in this small cohort still suffered from quantifiable sequel of the disease.

1. INTRODUCTION

Twelve patients were admitted to our intensive care with H1N1 pdm09 infection at the time of H1N1 pandemic (December 2010/January 2011). All these twelve patients were admitted within a period of two months. Severity of the disease ranged from mild to severe with multi organ impairment. All of these patients required some form of invasive intensive care support, including respiratory support, renal replacement therapy and extracorporeal support. Most of these patients were young or middle aged, with no prior intensive care admissions before the influenza infection. Four of the seven patients had predisposing factors including obesity, immunosuppression and one was peripartum. All survived and were discharged home after prolonged intensive care treatment.

There have been several studies identifying the epidemiology, risk factors associated with morbidity and mortality and treatment of H1N1 pdm09 infection [1]. There are also a number of studies looking at the respiratory [2-4] and neurocognitive [5,3,4] functions of survivors of ARDS who required prolonged intensive care treatment and ventilation. These studies clearly showed reduced neurocognitive function and restrictive lung function changes with a definitive reduction in the quality of life in that cohort of patients. There is not enough evidence in long term outcome of patients who had suffered H1N1 pandemic infection [6,7].

1.1 Aim

This is a one year follow up case series study to evaluate any impairment in respiratory, cardiac, renal function and neurocognitive assay in this cohort of patients, who had suffered and were treated for H1N1 infection.

2. METHODS

Ethical approval was obtained from University of Limerick Hospital ethical board. This study was performed in intensive care unit, Mid-Western Regional Hospital Limerick, Ireland.

2.1 Inclusion Criteria

Patients admitted to Mid Western Regional Hospital intensive care unit in the month of December 2010 and January 2011 with H1N1 pdm09 infection and consented to participate in the study.

Since this was a follow up study, all the patients were contacted over phone and by post to participate in the study. The letter contained information leaflets, consent form and invitation to attend the clinic. Seven of the twelve patients consented for the study and five declined to attend our clinic for the follow up study. Two among these five patients were not normally resident in this country and had returned to their domicile. All these five patients were happy to be interviewed over phone and also consented for us to contact their general practitioners to enquire regarding their health status.

In our clinic we assessed these patients for respiratory, cardiac, neurocognitive and renal function. SOFA scores were taken from health records at the time of ICU admission.

2.2 Respiratory Function

Pulmonary function tests, Chest X –Ray, High Resolution Lung CT (Computed Tomography) scan and six minutes walk test were performed to assess respiratory function. Pulmonary function testing was performed with measurements of spirometry, lung volumes

(Helium Dilution) and gas diffusion [Jaeger PFT (pulmonary function test) Masterscreen]. Chest X-Ray and high resolution CT were performed to identify any lung parenchymal or airway damage due to the disease process. CT examinations were performed using a 64 slice MDCT scanner (Somatom Sensation 64, Siemens Medical Solutions, Erlangen, Germany). Routine departmental High Resolution Computed tomography protocol (HRCT) was employed. One experienced radiologist with 8 years of experience of reading HRCT reviewed all of the HRCT examinations

2.3 Six Minute Walk Test

A premarked flat level corridor of the hospital, 100ft in length, was used for the six minute walk test. This was performed according to the American Thoracic Society guidelines [8]. Oxygen saturation, heart rate, blood pressure, body weight and height were measured before the beginning of the test. The pulse oximeter used was Nelcor Ect. The heart rate and oxygen saturation were also measured at the end of the test. Recent myocardial infarction (within a month), high blood pressure (systolic >180 mm of hg, diastolic > 100 mm of hg) or tachycardia (pulse >120/minute) precluded performing the walk test. A doctor or nurse accompanied the patients throughout the performance. Defibrillator trolley and emergency medication were immediately available if needed.

Predicted distance was calculated using the equation:

Men (7.57 x height in centimetre) – (5.02 x age) - (1.76 x weight in kg) – 309 m
Female (2.11x height in centimetre) - (2.29x weight in kg) – (5.78 x age) +667 m

Percentage of predicted distance was calculated according to the distance covered, which gave an assessment to their exercise capacity. A fall in SpO2 of more than 4 percent (ending below 93 percent) was defined as significant desaturation.

2.4 Cardiac Functions

Electrocardiography (ECG) and transthoracic echocardiography was performed, which aimed predominantly to assess right heart function. ARDS patients or patients with chronic respiratory disease (e.g. COPD), may have compromised right ventricular function. All

Echocardiography was performed by a single investigator who had certification in echocardiography (European Diploma in Adult Echocardiography).

2.5 Renal Functions

Renal function was assessed by performing serum urea and electrolytes. Given the time constraints involved in an outpatient study, we elected not to measure creatinine clearance. Creatinine Clearence was subsequently calculated based on their age, weight and serum creatinine level. Full blood count was also performed to identify any abnormalities.

2.6 Neurocognitive Function

Addenbrooke's cognitive examination (ACE-R) final revised version A (2005) was administered at 12 months post discharge from ICU of H1N1 pdm09 infected patients. It assesses attention & concentration, memory, language, verbal fluency, and visio-spatial ability. To assess verbal fluency, patients were required to say as many words as possible in two different categories (semantic and phonemic) and were scored accordingly. ACE-R also incorporates commonly used cognitive screening tool – MMSE (mini mental state examination).

Cut off <88 gives 94% sensitivity and 89% specificity for dementia.
Cut off <82 gives 84% sensitivity and 100% specificity for dementia.

Emotional functioning was assessed using Beck's depression inventory (BDI) and Beck's anxiety inventory (BAI). BDI score of 1-10 is considered normal, 11-16 mild mood disturbance, 17-20 borderline clinical depression, 21-30 moderate depression, 31-40 severe depression, over 40 extreme depression. BAI score of 0-21 indicative of very low anxiety, 22-35 moderate anxiety, greater than 35 indicate severe anxiety. Quality of life was assessed using General health questionnaire (GHQ). It is 12 question mental health portfolio used in variety of clinical situations. Higher scores indicate poor quality of life.

3. RESULTS

Of the seven patients participating in the study, three had pulmonary function testing indicating significant parenchymal lung injury. Two (Patient No. 1 and No. 5) had moderately severe

restrictive lung disease with impaired gas exchange (Table 1). One of these patients (Patient No.5) had significant desaturation while performing the six minute walk test (the full six minute of walk test however was completed). This patient was already attending the respiratory service and his respiratory function has much improved since discharge. One of the three (Patient No. 3) had mild impairment of his gas diffusion but with normal lung volumes; he also had significant desaturation with exercise. None of these parameters correlated with duration of ventilation nor did it correlate with receiving ECMO. Two of the patients with moderate to severe restrictive lung disease, demonstrated imaging findings consistent with post- ARDS fibrosis [9]. In both the cases, HRCT findings were similar with predominantly bibasilar, pulmonary fibrosis characterized by reticular thickening of the interstitium and traction bronchiectasis. No previous imaging was available for comparison.

Cardiac evaluation showed no evidence of right ventricular disease. Clinically none of the patients had symptoms consistent with cardiac dysfunction.

Three out of the seven patients needed renal replacement therapy during their treatment. One of the three patient continued to have impaired renal function based on their blood urea, electrolyte and creatinine clearance. None of the cohort had known renal impairment prior to admission (Table 1).

All patients cooperated fully with neurocognitive assessment procedure and none appeared unduly anxious during assessment. Neurocognitive functions could not be performed on one patient due to poor understanding and communication in English (Table 2).

Patients appeared cognitively intact using MMSE as screening tool. On MMSE, all patients scored 28 or greater, four patients scored 30/30. But on further testing using ACE-R, two (patient 1and 6) out of six has a score indicative of cognitive impairment. Both patients with cognitive impairment had difficulty with their memory. Five (patient 1, 3, 5, 6 and 7) out of six patients had evidence of phonological fluency impairment which was tested using category and word fluency. Impaired phonological fluency is well documented in schizophrenic and demented patients. This is also reported in post hypoxic

brain injury or in people exposed to low partial pressure of oxygen in high altitudes [10].

Visio-spatial skill was intact in all except in patient one who also had cognitive impairment. Patient 3, who did not meet cut off criteria for cognitive impairment, showed some impairment with memory & phonological fluency. All patients demonstrated good attention and calculation during cognitive testing. Two (patient 1 and 3) of the three patients, who had received ECMO had impaired neurocognitive functions and also poor quality of life. Half (patient 1, 5 and 7) of patients had scored high on GHQ indicating poor quality of life post H1N1 pdm09 infection. But none of patients met criteria for anxiety or depression using Beck's anxiety & depression inventory.

Five patients who had refused to participate in the study were interviewed over phone along with their general physicians to correlate the findings. One patient had suffered cerebrovascular accident while on ECMO. He had a residual left sided hemiplegia with mild visual loss. He was undergoing active rehabilitation. The other four had no medical co morbidities and two had returned to work (Table 1). They could not be evaluated regarding their neurocognitive function over phone.

4. DISCUSSION

Prolonged critical care admission and ventilation is associated with several complications[3]. Some of the complications could be due to the underlying disease process while the rest are associated with intensive care therapeutic modalities like prolonged ventilation, side effects of extracorporeal system, renal impairment due to prolonged hypoperfusion state or continuous exposure to nephrotoxic drugs and impaired neurocognitive functions [3,11,4]. One of our previously healthy young patient's had suffered cerebrovascular accident with left sided hemiplegia and visual loss while on extracorporeal system. One out of our three patients who had received renal replacement therapy continued to have chronic renal impairment and was followed up by the nephrology team. Three patients continued to have reduced respiratory functions including two who had developed pulmonary fibrosis. Both had reduced physical capacity and activities due to respiratory impairment and did not return to work [3,4,8]. These respiratory changes did not correlate with ECMO, or duration of ventilation.

Table 1. General demography of the patients along with their results of pulmonary function test and creatinine clearance

Patients	Age	SOFA score	NIV	IPPV	HFOV	ECMO	FEV1(L -% predicted)	FVC(L -% predicted)	TLC-He (L -% predicted)	DLCO % Pred (mmol/m/kpa)	6 min walk test (mts) (% predictive)	SPO$_2$ at 6 mins minute	CRRT	CC (mg/ml)
1	60	5	No	Yes	yes	Yes	90.4	91.3	66.1	64.1	310 (76.39%)	98%	Yes	130.6
2	55	4	Yes	No	No	No	95.5	94.3	95.5	82.51	510 (87%)	98%	No	102.06
3	26	9	No	Yes	Yes	Yes	105.4	97.3	98.6	62.6	460 (62.7%)	88%	Yes	104.63
4	27	3	Yes	No	No	No	92.7	90.6	93.62	84.32	540 (79.2%)	98%	No	124.73
5	56	7	No	Yes	No	Yes	80.9	81.8	67.2	40.5	550 (99.7%)	86%	Yes	65.19
6	45	10	Yes	Yes	Yes	No	96.8	105.4	93.8	77.6	540 (72%)	98%	No	85.65
7	44	3	Yes	No	No	No	114.1	106.3	100	76.4	600 (88.5%)	90%.	No	126.31

NIV – Non Invasive Ventilation, IPPV – Intermittent Positive Pressure Ventilation, HFOV- High Frequency Oscillatory Ventilation, CRRT- Continuous Renal Replacement Therapy, CC- Creatinine Clearance.
HRCT – High Resolution CT Scan, SOFA – Sequential Organ Failure Assessment Score, FEV – Forced Expiratory Volume. TLC – Total Lung Capacity

Table 2. Results of the depression, anxiety and neurocognitive assay

Patients	Age	GHQ	BAI	BDI	MMSE (30)	Attention & orientation(18)	Memory (26)	Fluency (14)	Language (26)	Visio-spatial skills (16)	ACER (100)
1	61	18	8	9	28	18	19	8	23	13	85
3	27	6	0	2	30	18	22	8	25	16	89
4	27	4	2	3	30	18	26	11	26	15	96
5	56	14	3	5	29	18	24	9	26	16	93
6	45	9	0	0	30	18	25	9	26	16	94
7	45	16	2	7	30	18	19	6	24	16	83

GHQ-General Health Questionnaire; BAI –Beck's Anxiety Index; BDI- Beck's Depression Index; MMSE –Mini Mental State Examination; ACE-R - Adenbrooke's Cognitive Examination –revised

Five of our patient's had impaired phonological fluency. These patients did not have any past record of phonological disorder. This could signify hypoxic brain injury during their period of treatment, if this was a new development, similar to findings in Paolaa et al. [10] study. None of the patients had suffered from depression, though two of them had slightly reduced neurocognitive functions and three had decreased feeling of well being. Though our study group was small, the findings were similar to Hopkins et al. [2] study which showed reduced long term neurocognitive functions in patients who had suffered critical illness including ARDS which included depression and anxiety [3,5].

As the number of patient in this study was very small, it was not possible to correlate outcome to therapies required during their illness. The number of patients was very small, which attributed to the weakness of the study. Even in this small cohort, approximately two third of the patient couldn't go back to work and lead a normal life which signifies the severity of the disease process and its sequel.

5. CONCLUSION

H1N1 Pandemic 09 was essentially a new disease causing severe respiratory failure with difficulty with oxygenation ad ventilation. Given the severity of their illness and the length of ICU admission, we were keen to see how our cohorts were one year post admission.

Though this was a small cohort of twelve patients, like many other critically ill patients, some of these patients continued to have significant residual disease like permanent neurological deficit, impaired phonological fluency, restrictive lung disease and renal impairment and poor quality of life.

A larger cohort of patients or a nationwide study would help us evaluate the effect of H1N1 infection on the patients admitted during the two major outbreaks in 2009/2010 and 2010/2011. The nature of the flu virus and seasonal variations can have a major impact on our health service, as the H1N1 pdm09 in those two years did. Each new pandemic will bring no doubt different experiences, but we need a medical community to learn as much as possible from each event to help inform us as much as possible and also to help manage the effects each new variant as they will no doubt emerge.

ETHICAL APPROVAL

ACKNOWLEDGEMENTS

FUNDING

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Vaillant L, La Ruche G, Tarantola A, Barboza P. Epidemiology of fatal cases associated with pandemic H1N1 influenza. Eurosurveillance. 2009;14(33).

2. Hopkins R, Lindell K Weaver, Karen J Chan, James F Orme Jr. Two-year cognitive, emotional, and quality-of-life outcomes in acute respiratory distress syndrome. American Journal of Respiratory and Critical Care Medicine. 2005;171:340-347.

3. Joan R Mascla, Oriol Roca, ferran Torres. Quality of life, pulmonary function, and tomography scan abnormalities after ARDS. Chest. 2011;139(6).

4. Herridge MS, Tomlinson G. Functional disability 5 years after acute respiratory distress syndrome. New England Journal of Medicine. 2011;364(14).

5. Hopkins R, Jackson JC. Long – term neurocognitive function after critical illness. Chest. 2006;130(3):869–878.

6. Lynfield R, Davey R, Dwyer DE, Losso MH, Wentworth D, Cozzi-Lepri A, Herman-Lamin K, Cholewinska G, David D, Kuetter S, Ternesgen Z, Uyeki TM, Lane HC, Lundgren J, Neaton JD. INSIGHT Influenza study group. Outcomes of influenza A (H1N1)pdm09 virus infection: Results from two international cohort studies. PLoS One. 2014;9(7):e101785.

DOI: 10.1371/journal.pone.0101785. eCollection 2014.

7. Matthias Pierce, Jennifer J Kurinczuk, Patsy Spark, Peter Brocklehurst, Marian Knight, Perinatal outcomes after maternal 2009/H1N1 infection: National cohort study. BMJ. 2011;342.
DOI:http://dx.doi.org/10.1136/bmj.d3214 (Published 14 June 2011) Cite this as: BMJ 2011;342:d3214.

8. ATS Statement: Guidelines for the six minute walk test. American Thoracaic Society; 2002.

9. Li P, Zhang J-F, Xia X-D, Su D-J, Liu B-L, Zhao D-L, Liu Y, Zhao D-H. Serial evaluation of high-resolution CT findings in patients with pneumonia in novel swine-origin influenza A (H1N1) virus infection. The British Journal of Radiology. 2012;85: 729–735.

10. Paolaa MD, Bozzalia M, Faddab L, Musiccoc M, Sabatinid U, Caltagironeb C. Reduced oxygen due to high-altitude exposure relates to atrophy in motor-function brain areas. European Journal of Neurology; 2008.

11. Guangxi, Chakradhar V. Eight year trend of acute respiratory distress syndrome. American Journal of Respiratory and Critical Care. Med. 2011;183.

_____