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RESEARCH ARTICLE

DERANGEMENT OF BLOOD CHEMISTRY SPECIFICALLY LIVER FUNCTION TESTS AND RENAL FUNCTION TESTS IN INFLUENZA A/H1N1 INFECTION

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ABSTRACT

Objective: To determine the multi-organ effects of influenza A/H1N1 virus, particularly focusing on the derangement of hepatic and renal function during the course of the infection.
Design: Cross sectional study
Place and duration of study: Department of Chemical Pathology and Endocrinology Combined Military Hospital, Multan, from Nov 2017 to Jan 2018.
Patients and Methods: All suspected cases with clinical features of influenza flu, who were admitted in Combined Military Hospital Multan, from Nov 2017 to Jan 2018 were closely observed for the purpose of investigating the multi-systemic effects of the disease.PCR for influenza virus was conducted. Liver function tests and renal function tests were performed in all suspected cases. In A/H1N1 positive cases LFTs and RFTs were repeated after completion of treatment with oseltamavir and azithromycin. A/H1N1 positive and negative groupswere compared.A total of 145 cases were analyzed.
Results: Out of the 145(100%) cases that had been reviewed, 72 (49.65%) cases were positive for influenza A/H1N1 infection, 73 (50.35%) patients had negative results for influenza virus. Out of the positive 72(100%) cases, 18(25.1%) had deranged LFT'S, 15(20.83%) had deranged RFT's and 10(13.8%) had both LFT'S and RFT'S deranged, and the remaining 29(40.27%) patients had normal chemistry. While the 73 patients with negative results for H1N1 virus had normal chemistry and no derangement of LFT'S and RFT'S. Our patients were treated for H1N1 infection, and the liver and kidney function reverted back to a normal level in 72 hours.
Conclusion: Our study showed that significant number of patients with influenza A/H1N1 infection had derangement in LFTS and RFTS as compared to non –influenza flu cases indicating that it is a multi-organ effecting virus. Early initiation of treatment resulted in reversion of deranged LFTs and RFTs

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INTRODUCTION

The outbreak of the influenza A/H1N1 virus has been declared as a great challenge for the healthcare systems worldwide, labeled as the first pandemic of 21st century by the WHO, due to its rapid spread and clinical severity (Fineberg, 2009). Global morbidity and mortality stats are based primarily on the recognition of respiratory symptoms. But various case reports and epidemiologic studies have shown diverse phenotypic presentations of influenza infection due to involvement of organ systems other than respiratory tract (Sellers *et al.,* 2017). The most frequently described clinical entities are viral myocarditis (Ukimura *et al.,* 2013; Iwanaga *et al.,* 2014; Ludwig *et al.,* 2015) and viral encephalitis (Goenka *et al.,* 2014; Mizuguchi, 2013; Simon *et al.,* 2013; Jeganathan *et al.,* 2013; Chan and Ng, 2014). The virus is also known to have a negative effect on the function of other vital organs like liver (Soleimani *et al.,* 2017), kidneys (Bagshaw *et al.,* 2013), gastrointestinal tract and skeletal muscles (Desdouits *et al.,* 2013). Influenza A virus is a single-stranded ribonucleic acid

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(RNA) virus, it has many subtypes and genomic variations depending on the presence of surface glycoproteins, haemagglutinin (HA) and neuraminidase (NA). It usually affects the respiratory tract endothelium and its shedding lasts for 2–5 days after the appearance of its symptoms. However influenza infection is frequently associated with a number of clinical syndromes that involve organ systems outside the respiratory tract.In some patients multiple organ dysfunction syndrome (MODS) may develop and they die. Although it is well known that the majority of the viral- induced tissue damage is caused by an inflammatory cytokine storm and oxidative stress (Bradley-Stewart *et al.,* 2013; Teijaro *et al.,* 2014) but direct H1N1 viral organ injury has not been completely ruled out (Rothberg and Haessler, 2010; Parisi Lister *et al.,* 2009; Kumar *et al.,* 2009). Mostly the health care providers focus on the respiratory complications due to H1N1 infection and overlook possible multi-organ involvement. Recognition of these extra-pulmonary complications is critical for early initiation of anti-viral therapy and organ- specific supportive care. A/H1N1 is still susceptible to neuroaminase inhibitors (oseltamivir and zanmivir). Disease severity, length of illness and mortality can be reduced by use of Oseltamivir (Jefferson *et al.,* 2014). Present study was conducted with the objectives to monitor LFTs and RFTs for early detection ofmulti-systemic damage caused by Inflluenza A/H1N1 infection particularly liver and kidney injury. We compared liver and kidney injury between influenza A/H1N1 positive and negative groups as well as effect of early initiation of treatment with oseltamavir and supportive care.

PATIENTS AND METHODS

We conducted an observational cross sectional study by choosing all suspected cases of influenza infection that were admitted in CMH Multan from November 2017 – January 2018. Non probability consecutive sampling technique was used for collection of our data. We excluded all known cases of chronic kidney diseases and liver diseases (hepatitis, cirrhosis, fatty liver disease). The study was conducted on 145 patients, both male and females, from the age group of 02 years to 80 years with the suspicion of influenza flu. All hospitalized patients were subjected to nasopharyngeal swabs which were kept in viral transport medium. RT-PCR for pandemic H1N1 virus was carried out using kits supplied by National Institute of Health according to manufacturer's instructions. First through specific primers and probes for the detection of influenza type A, if viral infection was diagnosed then by using specific primers and probes for subtypes of influenza A, H1N1 diagnosis was performed. All patients, both positive and negative on the testing of Real Time Polymerase chain reaction, were subjected for liver function tests (Serum Bilirubin, ALT, ALP) and renal function tests (Serum Urea, Creatinine) to confirm a relationship between H1N1 virus and liver and kidney injury. LFTs and RFTs were performed on Selectra E fully automated chemistry analyzer using kits by Diasys and Human. Patients were followed up and LFT'S and RFT'S were repeated after treatment. Results were compared between influenza A/H1N1 positive and negative groups. All the data including biochemical parameters was entered and analyzed by using statistical package for social sciences version 20. Descriptive statistics for qualitative variables like gender were calculated in percentages. Mean and SD were calculated for all quantitative variables like age, LFTS and RFT'S. P value less than 0.05 was considered as significant.

RESULTS

Out of the total 145(100%) cases that had been reviewed, 72 (49.7%) cases were positive for influenza A/H1N1 infection, 73 (50.3%) patients had negative results for influenza virus. Out of the total 145(100%) cases, we had 90 (62.1%) male patients and 55 (37.9%) female patients. In 72(49.7%) positive patients; we had 49 (33.8%) male patients and 23 (15.9%) female patients. While out of the 73(50.3%) negative H1N1 cases, we had 41 (28.3%) male patients and 32(22.0%) female patients. It was observed from our results that H1N1 infection was more prevalent among males than females. It could be due to their outdoor activity, and to work in health-care occupations, which may increase their exposure rate to influenza flu as compared to females who stay at home (Fig. 1). Our study included patients from the age group of 2 years to 80 years; among the positive 72(49.7 %) H1N1 cases, 5(3.4%) persons had less than 10 years age, 27 (18.6%) of them had the age ranged between 10 to 30 years, and 24 (16.5%) persons were between 31 to 50 years of age and 16(11.2%) were between 51 to 80 years of age. While in the negative 73 (50.3%) cases, 4(2.8%) persons had less than 10 years of age, 29 (20.0%)were between 10 -30 years of age, 26(17.9%) had the age ranged between 31 -50 years and remaining 14(9.7%) had the age between 51- 80 years (Fig. 2).

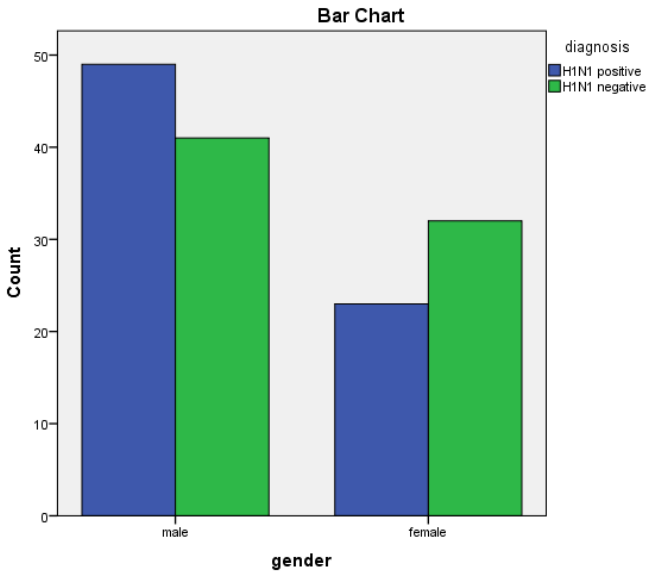

Fig. 1. Gender distribution among Influenza A/H1N1 positive and negative groups

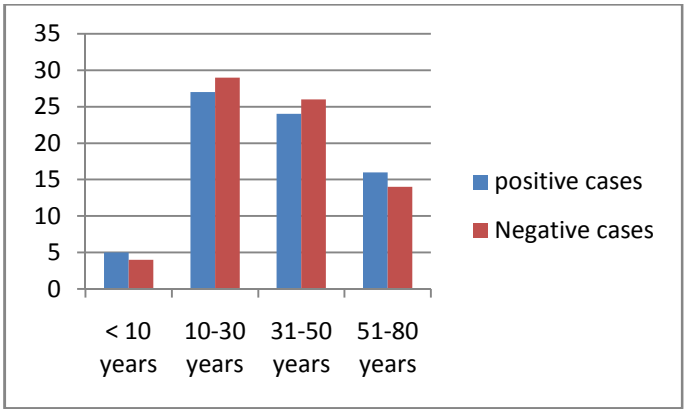

Fig. 2. Age Distribution among H1N1 positive and negative cases

Table1. LFTs and RFTs in Influenza A/H1N1 negative cases (n=73)

Parameters	Minimum	Maximum	Mean	Std. Deviation
ALT	8.00	42.00	32.1233	7.25516
total bilirubin	5.60	17.30	14.3863	2.50285
Creatinine	5.00	106.00	85.4521	14.46456
urea	2.70	8.90	6.6425	1.25896
ALP	56.00	301.00	216.4658	57.77088

Table2. LFTs and RFTs in Influenza A/H1N1 positive cases (n=72)

Parameters	Minimum	Maximum	Mean	Std. Deviation
ALT	24.00	176.00	63.1429	30.99219
total bilirubin	11.80	54.00	17.1619	6.04063
ALP	155.00	349.00	265.3095	55.02793
urea	6.60	18.90	10.0548	3.44385
Creatinine	75.00	297.00	129.8333	51.70739

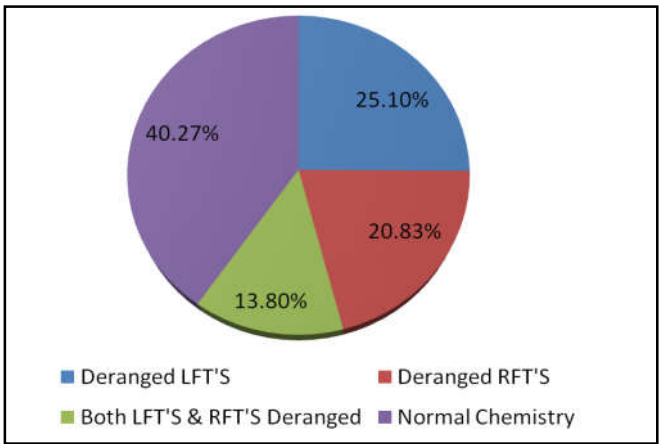

Fig 3. Overview of blood chemistry in Influenza A/H1N1 positive group

When we collected and compiled our results, we found that liver function tests were deranged in the group with positive H1N1 infection. Moreover, a positive correlation between H1N1 virus and deranged renal parameters was also noticed. When we compared RFTS and LFTS test results between the influenza positive and negative group in order to establish a relationship between influenza A/H1N1 infection and liver and kidney dysfunction. We found a significant derangement of RFT'S and LFT'S in positive H1N1 group. While h1n1 negative group had normal chemistry and no (0 %) derangement of LFT'S and RFT'S. This difference was statistically significant (p value<0.05).Overall view of Blood chemistry in H1N1 positive cases is shown in (fig3). Details of renal and hepatic parameters in H1N1 negative and positive groups are shown in (Table1) and (Table2) respectively. In H1N1 positive cases mainly ALT showed derangement rising up to two folds, bilirubin and ALP showed mild derangement only in few cases. Urea and Creatinine were mildly derangement in most of the cases. Hence our study demonstrated a positive correlation between derangement of LFT'S and RFT'S in H1N1 positive group as compared to H1N1 negative group. Patients were hospitalized early in the course of their disease and their parameters returned back to the normal level after treatment.

DISCUSSION

Our study strongly supports the hypothesis that Influenza A/ H1N1 is a multi-organ effecting virus. It also affects liver and renal function of patients other than respiratory function. Our findings concluded that significant number of patients with influenza A/H1N1 infection had derangement in LFTS and RFTS as compared to non –influenza flu cases. Although different studies have revealed conflicting results in this regard but Seretis C et al who performed review of various published clinical studies have finally concluded that A/H1N1 virus impair the function of all vital organs and trigger the cascade of systemic inflammation and it should be regarded as potentially hepatotropic (Seretis *et al.,* 2013). We observed that early initiation of treatment with oseltamavir and supportive care resulted in reversion of deranged LFTs and RFTs. Similarly A. Hamzic-Mehmedbasic *et al.* in their case report highlight the importance of recognizing the pulmonary and extra pulmonary complications of influenza A/H1N1 infection as early intervention and management can result in full recovery even in a case of the critically ill patient (Hamzic-Mehmedbasic *et al.,* 2015). Influenza A/H1N1 virus usually affects the respiratory tract, involvement of other systems by the virus is considered rare. However, studies have reported the presence of extensive centrizonal hemorrhagic necrosis of the hepatocytes, along with the existence of sinusoidal dilatation in severe cases of influenza A/H1N1 infection (Bal *et al.,* 2012). The pathogenesis is not yet fully understood, numerous studies have emphasized that influenza A /H1N1 virus can affect any organ as an outcome of response to viral antigens and stormy release of cytokines that can cause direct liver injury per se (Morales-Garcia *et al.,* 2012). We compared the seasonal influenza and influenza A/H1N1 positive group and found a significant derangement of RFT'S and LFT'S in positive H1N1 group. Papic et al had a similar finding in their study especially the transient character of the liver injury, which was consistent with the severity of the infection and resolved at the stage of remission (Papic *et al.,* 2012). Likewise there are studies which have analyzed involvement of kidneys, especially acute kidney injury (12,21,25). According to one study, Acute kidney injury is more frequently present in patients with severe H1N1 infection, and is more commonly associated with hemodynamic instability, advanced age, obesity, diabetes mellitus and rhabdomyolysis. However the exact pathogenesis of disease is still not understood. H1N1 has been considered as a threat to severe respiratory tract infections and pulmonary complications. Therefore, the involvement of other organs and the occurrence of hepatic and renal injury due to H1N1 infection have been overlooked.

Conclusion

We conclude that significant number of patients with influenza A/H1N1 infection had derangement in LFTS and RFTS as compared to non –influenza flu cases indicating that it is a multi-organ effecting virus. Early initiation of treatment with oseltamavir and supportive care resulted in reversion of deranged LFTs and RFTs in influenza A/H1N1 positive patients. LFT'S and RFT'S should be closely monitored during the course of infection, so that instant treatment plan of renal and liver protection could be applied.

Recommendations

There is a need for better understanding the mechanisms involved in the pathogenesis of acute kidney dysfunction and liver involvement in these patients. Further studies are suggested, regarding monitoring of multi-organ involvement

due to the virus along with establishment of definite cut off values of LFT'S and RFT'S as prognostic markers.

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