COMPARATIVE ANALYSIS OF CLINICAL AND LABORATORY SIGNS OF LUNGS AFFECTION IN PATIENTS WITH COVID-19 WITH THOSE OF PANDEMIC INFLUENZA A/H1N1

K.V. Yurko[1], D.V. Katsapov[1], A.V. Bondarenko[1], V.E. Kulshin[2], O.I. Chirukina[2]

[1]Kharkiv National Medical University, Kharkiv, Ukraine
[2]CNE KRC Regional Clinical Infectious Diseases Hospital, Kharkiv, Ukraine

https://doi.org/10.35339/ic.9.1.19-23

Abstract
Influenza viruses, in particular A – A(H3N2) and A(H1N1)pdm09, as well as influenza B virus, mainly (98%) of the B/Victoria line, continue to circulate during the current epidemic season. The level of influenza vaccination remains low, about 0.6% of the population of Ukraine, and among occupational and epidemiological risk groups – 22.8%, according to the Public Health Centre of the Ministry of Health of Ukraine. In the COVID-19 pandemic, simultaneous circulation of influenza viruses and SARS-CoV-2 can lead to difficulties in differential diagnosis and treatment. Comparison of clinical and laboratory features of severe influenza complicated by pneumonia caused by pandemic influenza virus A(H1N1)pdm09 in the epidemic season of 2015/2016 Kharkiv RCIDH with COVID-19 on clinical and laboratory data was the aim of the work. **Patients and research methods.** The analysis of clinical symptoms and laboratory examination data of 19 patients with influenza complicated by community-acquired pneumonia of clinical group IV who were treated at the Kharkiv Regional Hospital and their comparison with those of patients with COVID-19 according to the literature. **Results and discussion.** Among the studied patients, men predominated – 12 persons (63.2%) aged 50.68±11.95 years. The predominant number had concomitant diseases. At the beginning of the disease, moderate weakness, headache, fever, minor catarrhal phenomena and, as a result, delayed hospitalization prevailed. From 3–4 days of the disease the condition significantly worsened, shortness of breath and cyanosis joined. Typical initial symptoms of COVID-19 are fever of varying degrees (73%), unproductive cough (59%) and shortness of breath or shortness of breath. **Conclusions.** In patients with COVID-19 and severe influenza, a more acute onset of the disease was reported, with moderate weakness, headache and fever up to 38°C and symptoms of pharyngitis. Influenza patients often show a delay in seeking medical attention and hospitalization for 6.21±1.46 days of illness. The severity of the disease in influenza is due to the accession of community-acquired pneumonia, in contrast to COVID-19, where the typical features are diffuse, mostly subpleural lung affection. Vaccination of people at risk before the start of the epidemic season is necessary to prevent severe complications of influenza caused by the pandemic virus A(H1N1)pdm09 in the context of the COVID-19 pandemic.
Key words: *influenza, pneumonia, COVID-19, diagnosis.*

INTRODUCTION

According to the WHO European office, influenza activity, based on patients in sentinel primary care settings testing positive for influenza virus infection, crossed the epidemic threshold of 10% set for the region in week 49/2021. For the region as a whole influenza activity had been increasing, with different levels of activity across the countries and areas of the region, with a dominance of A(H3) viruses [1] that each year infects approximately ten to thirty per cent of European population, and causes hundreds of thousands of hospitalizations across Europe. Both influenza type A and type B viruses were detected with a dominance of A(H3) viruses across all monitoring systems and in all cases. For week 49/2021, 185 (11%)

Corresponding Author:
Dmytro Katsapov, MD, PhD, Associate professor of the Department of Infectious Diseases, Kharkiv National Medical University, Ukraine.
E-mail: Dkatsapov@ukr.net

of 1 650 sentinel specimens tested positive for an influenza virus; 182 (98%) were type A and 3 (2%) were type B. Of 67 subtyped A viruses, 3% were A(H1N1) pdm09 and 97% A(H3) [2]. Older people, younger children and those with chronic conditions suffer the most, but everyone is at risk of developing serious complications – which include pneumonia, myocarditis and encephalitis – that may result in death [3].

According to the Centre for Public Health of the Ministry of Health of Ukraine, and data of the results of laboratory research by PCR in 13 of 45 samples of materials in the last epidemic season identified influenza viruses: 6 – type A(H1) pdm09, 2 – type A(H3), 3 – type A not subtyped and 2 – type B [4]. It is noted that in the context of the COVID-19 pandemic, monitoring of the data may be inaccurate, both due to the difficulty of differential diagnosis and the reduction in the number of studies for seasonal respiratory viruses' detection.

During the last epidemic season of 2020 in Kharkiv region, 72,936 people fell ill with acute respiratory viral diseases (ARVD) and influenza in the region – 2.8% of the regional population. The largest proportion of patients was registered in the age group 5–14 years. The incidence rate in the region was 57.4% lower than the epidemic threshold and 8.2% lower compared to the incidence rate for the same period in 2019.

According to the Center for Public Health of the Ministry of Health of Ukraine, the level of influenza vaccination remains low, accounting for about 0.6% of the population of Ukraine, and among occupational and epidemiological risk groups – 22.8% of all those vaccinated [4].

However, circulation of influenza A(H1N1) pdm09 virus continues. This virus is known to differ from the already "classic" strains of influenza A1 in genetic and antigenic properties [5]. According to the world literature, the spectrum of clinical manifestations of this infection ranges from mild upper respiratory tract infection to the development of severe pneumonia [5, 6]. The onset of the disease mostly has no pathognomonic signs. In cases of lethal outcome, the deterioration of patients occurs on the 4th day of the disease due to the development with a subsequent lightning course of subtotal or total bilateral pneumonia with the phenomena of hemorrhagic pulmonary edema. Complicated forms of the disease are registered in patients of a group of risk, as a rule, in pregnant women, patients with chronic respiratory diseases, diabetes mellitus and cardiovascular diseases [7]. According to the world and domestic literature, delayed hospitalization and administration of neuraminidase inhibitors are a risk factor for complications and unfavorable course of influenza [8].

In modern conditions of pandemic, simultaneous circulation of influenza viruses and SARS-CoV-2 can lead to difficulties in differential diagnosis and treatment.

Thus, Ukraine takes the same situation as in other countries of the world – dominant has become more aggressive and pain contagious variant of the Delta, which requires more vigilant conducting anti-epidemic health authorities [9].

According to our own data, the clinical picture of pandemic influenza during the 2009–2010 epidemic was also characterized by the onset of disease with moderate intoxication and fever and minor upper respiratory tract affection, leading to delayed hospitalization and specific therapy, which is a risk factor for adverse events, especially in patients of risk groups [10].

Purpose, subjects and methods

1. The purpose of the study was to compere clinical and laboratory features of severe influenza complicated by viral pneumonia caused by pandemic influenza virus A(H1N1)pdm09 in the epidemic season of 2015/2016 CNE KRC Regional Clinical Infectious Diseases Hospital, Kharkiv with COVID-19 by clinical and laboratory data.

2. Subjects & Methods

The clinical symptoms and data of laboratory examination of 19 patients with influenza complicated by community-acquired pneumonia of the IV clinical group, who were treated in the CNE KRC Regional Clinical Infectious Diseases Hospital, Kharkiv during the epidemic season 10.2015–01.2016 were analyzed.

The average age of patients in the study group was 50.68±11.95. Among the patients of the experimental group, men predominated – 63.2%.

In the period from 2015 to 2016, patients underwent clinical studies according to a unified clinical protocol (blood, urine, chest radiography, clinical and bacteriological analysis of sputum, creatinine, urea and biochemical blood tests in dynamics). Statistical data processing was performed using the program MS Excel 2010. Analysis of clinical and laboratory data of COVID-19 was performed as described in the literature.

Results and discussion

During the epidemic season of 2015–2016, there was a significant increase in the incidence of influenza-like illnesses. In January 2016, 235 people

with influenza-like illnesses were hospitalized. Influenza caused by undifferentiated virus was diagnosed in 108 patients, influenza complicated by pneumonia – in 35 patients. Influenza caused by pandemic strain A(H1N1)pdm09 by PCR and immunofluorescence was confirmed in 22 patients. The symptoms and laboratory parameters of 19 people with a confirmed diagnosis of influenza who died in the CNE KRC Regional Clinical Infectious Diseases Hospital, Kharkiv were analyzed.

The mean age of patients of the group was 50.68±11.95 years. Among the studied patients, men predominated – 12 people (63.2%). Concomitant chronic diseases were detected in the vast majority of patients (94.7%). In particular, 13 people (68.4%) were obese, 9 people (47.4%) had coronary artery disease, 7 people (36.8%) – arterial hypertension. Chronic kidney disease was observed in 5 patients (26.3%) and other chronic diseases in 6 (31.6%). In 6 people (31.6%) three or more chronic diseases were observed simultaneously. Thus, all patients of the cohort belonged to the risk group according to the criteria of the unified clinical protocol of medical care for influenza patients according to the Order of the Ministry of Health of Ukraine on July 16, 2014 No.499 "On approval and implementation of medical – technological documents for standardization of medical care for influenza and acute respiratory infections". Data on prophylactic influenza vaccinations are not available in all patients.

Late admission to the hospital was very typical, and as a result, hospitalization was delayed – 6.21±1.46 days from the onset of the disease. This can be partly explained by the fact that the first symptoms of the disease were mainly: moderate weakness in 94.7% of cases, moderate headache – in 89.5%. The temperature at the beginning of the disease was mostly up to 38°C in 17 patients (89.5%). Airway lesions during the first day were characterized by moderate throat pain and discomfort in 7 patients (42.1%), moderate dry cough was reported in all cases. Hyperemia of the pharyngeal mucosa was observed in 13 patients (68.4%). Mucous secretions from the nasal passages were noted by only 5 patients (26.3%).

Thus, in most cases, the onset of the disease was relatively mild, thus the patients did not seek for medical help in time. All of them received only symptomatic treatment. According to the history, 7 patients (36.8%) at the beginning of the disease refused to be hospitalized. A threatening factor is that patients with widespread lung damage in the first 3–4 days subjectively felt well and often tried to refuse treatment. This dissonance, as well as the lack of characteristic stethoacoustic signs of pneumonia at the beginning of the disease is also noted by other authors [11]. But, from days 3-4, the disease was accompanied by fever above 39.1ºC in 11 cases (57.9%), attacks of painful cough, with blood in the sputum in 9 cases (47.4%) myalgia in 17 – (89.5%), nausea and vomiting – in 3 cases (15.8%). All patients noted the accession of shortness of breath during this period, cyanosis of the skin was observed in 9 (47.4%) patients.

At the initial examination, the condition was mostly moderate or severe, cyanosis of the skin and shortness of breath 33.7±9.01 per minute were observed. Tachycardia (106.2±28.3)/min, attenuation of heart tones was determined. Moist rales and crepitation were heard at auscultation in 18 patients (94.7%), percussion sound dulling in all cases. X-ray in all cases revealed bilateral pneumonia, lobar or sublobar in 18 patients (94.7%). The lower lobes of both lungs were mainly affected with further spread of infiltration despite antiviral and antibacterial therapy. SpO2 was 81.5±21.8% with a further decrease to 62.94± ±16.8%, despite the fact that all patients received oxygen therapy throughout their hospital admission. Liver enlargement was detected in 7 patients (36.8%). In the clinical analysis of blood, despite the severity of the condition and the duration of the disease, no significant inflammatory reaction was identified. The total number of leukocytes was 5.38±1.44·109/l, bent – 17.4±4.7%, segmented – 62.3±16.6%, lymphocytes – 17.5±4.7%, monocytes – 3.1±0.82%, ESR – 23.67±6.3 mm/hr. There was a moderate increase in urea 8.85 ± 2.36 mm/l and creatinine – 124.8±33.35 μM/l.

According to data of various researchers, common symptoms of influenza and COVID-19 are acute onset, dry cough and shortness of breath, which is associated with severe disease. Relatively mild onset of the disease with moderate symptoms of upper respiratory tract lesions is common. However, with COVID-19, development of lung damage and acute respiratory distress syndrome is observed on 7–9 day of the disease, which is significantly longer than same with influenza [12]. Typical initial symptoms of COVID-19 are fever of varying degrees (73%), unproductive cough (59%) and shortness of breath or feeling of lack of air. Taste disturbances and anosmia may appear on day 2–14 of the disease in 50–61.2% of severe cases [13]. However, these symptoms can also occur in 17.3% of people over

40 who have various chronic diseases. Computed tomography of the lungs plays an important role in the early diagnosis of severe forms of COVID-19. The most typical sign is opacity of the type of ground glass (65%) with affection from one to several segments of the lungs depending on the severity. In a significant number of severe forms of the disease the lesions were bilateral [12]. In contrast, in case of influenza caused by pandemic strain A (H1N1) pdm09, typical radiographic features are multifocal foci of consolidation. In the progress of the disease, the appearance of pleural effusion and cavity formation was possible. Involvement of four or more zones up to day 7 of the disease was considered one of the signs of adverse course [12, 14, 15].

Conclusions

1. COVID-19 and severe influenza are characterized by an acute onset of the disease, accompanied by moderate weakness, headache and fever up to 38°C. Upper respiratory tract affection was characterized mainly by symptoms of pharyngitis. Classic symptoms of tracheal lesions in influenza have not been reported. As a result, patients with influenza postpone admission to the hospital by 6.21±1.46 days from the onset of the disease.

2. All patients with adverse disease outcomes belonged to the risk group by age and the presence of comorbidities, mainly obesity, coronary heart disease, hypertension, and others. The further severity of influenza was due to community- acquired pneumonia, lobular or sublobular, mostly bilateral with characteristic stethoacoustic signs and symptoms of respiratory failure, in contrast to COVID-19, where the typical features are diffuse, mostly subpleural lung affection.

3. Vaccination of persons of risk groups before the beginning of the epidemic season is necessary to prevent severe complications of influenza caused by the pandemic virus A/H1N1pdm in the conditions of the COVID-19 pandemic, and to increase medical education of the population about behavior in case of symptoms of influenza appearance. Neuraminidase inhibitors should also be prescribed to persons at risk within 48 hours of the onset of the disease.

DECLARATIONS:

Statement of Ethics

The authors have no ethical conflicts to disclosure.

Consent for publication

All authors give their consent to publication.

Disclosure Statement

The authors have no potential conflicts of interest to disclosure, including specific financial interests, relationships, and/or affiliations relevant to the subject matter or materials included.

Funding Sources

There are no external sources of funding

Data Transparency

The data can be requested from the authors.

References

1. *Season overview (n.d.).* Retrieved December 24, 2021, from https://flunewseurope.org/SeasonOverview

2. European Centre for Disease Prevention and Control/WHO Regional Office for Europe. *Flu News Europe, Joint ECDC–WHO weekly influenza up date, week 49/2021.* [Online]. Retrieved from https://flunewseurope.org/Archives

3. European Centre for Disease Prevention and Control. *Seasonal influenza.* [Online]. Retrieved from https://www.ecdc.europa.eu/en/seasonal-influenza

4. *Zakhvoryvanist na grip ta GRVI v Ukraini* [*incidence of Influenza and AVRD in Ukraine]*. Center hromadskogo zdorovya [Public Health Center]. (2020). Retrieved October 11, 2020, from https://phc.org.ua/kontrol-zakhvoryuvan/inshi-infekciyni-zakhvoryuvannya/monitoring-i-ocinka/zakhvoryuvanist-na-grip-ta-grvi-v-ukraini.

5. Short, K. R., Kasper, J., van der Aa, S., Andeweg, A. C., Zaaraoui-Boutahar, F., Goeijenbier, M., … & Kuiken, T. (2016). Influenza virus damages the alveolar barrier by disrupting epithelial cell tight junctions. *European Respiratory Journal*, *47*(3), 954–966. https://doi.org/10.1183/13993003.01282-2015

6. Pérez-Carrasco, M., Lagunes, L., Antón, A., Gattarello, S., Laborda, C., Pumarola, T., … & CRIPS investigators (2016). Influenza infection in the intensive care unit: Four years after the 2009 pandemic. *Enfermedades infecciosas y microbiologia clinica*, *34*(3), 177–183. https://doi.org/10.1016/j.eimc.2015.04.004

7. Perez-Padilla, R., de la Rosa-Zamboni, D., Ponce de Leon, S., Hernandez, M., Quiñones-Falconi, F., Bautista, E., … & INER Working Group on Influenza (2009). Pneumonia and respiratory failure from swine-origin influenza A (H1N1) in Mexico. *The New England journal of medicine*, *361*(7), 680–689. https://doi.org/10.1056/NEJMoa0904252

8. Katsapv, D., Kozko, V., Bondarenko, A., et al. (2015). Analiz kliniko-laboratornych aspectiv pandemichnogo gryppu A (H1N1) ta yogo uskladnen v Kharkivskiy oblasty [Title of article]. In *Epidemiologia, ekologiya I gigiena*: *Proceedings of the Conference*, Kharkiv, 2011. (Pp. 108–112). Kharkiv: KNMU. [In Ukrainian].

9. Sanyaolu, A., Okorie, C., Marinkovic, A., Haider, N., Abbasi, A. F., Jaferi, U., … & Balendra, V. (2021). The emerging SARS-CoV-2 variants of concern. *Therapeutic advances in infectious disease, 8,* 20499361211024372. https://doi.org/10.1177/20499361211024372

10. Shi, H., Han, X., Jiang, N., Cao, Y., Alwalid, O., Gu, J., … & Zheng, C. (2020). Radiological findings from 81 patients with COVID-19 pneumonia in Wuhan, China: a descriptive study. *The Lancet. Infectious diseases*, *20*(4), 425–434. https://doi.org/10.1016/S1473-3099(20)30086-4

11. Yurko, K. V., Katsapov, D. V., Bondarenko, A. V., Nartov, P. V., Maksul, T. Y., & Harchenko, O. M. (2021). Kliniko-laboratorna haracteristica letalnich vipadciv vid pandemichnogo gripu A/H1N1 porivnjano z tyagkimi formami COVID-19 [Clinical and laboratory characteristics of lethal cases of pandemic influenza A/H1N1 in comparison with severe forms of COVID-19]. *Infekciini hvorobi [Infectious diseases]*, (3), 21–26. https://doi.org/10.11603/1681-2727.2021.3.11432

12. Marlene, M. S., Singer-Cornelius, Th., Obere, M., Gengler, I., Brockmeier, S. J., & Sedaghat, A. R. (2020). Olfactory dysfunction and sinonasal symptomatology in COVID-19: 3 prevalence, severity, timing and associated characteristics. [Online]. Retrieved from https://www.entnet.org/sites/default/files/uploads/ sedaghat_2_olfactory_dysfunction_and_sinonasal_symptomatology_in_covid-19.pdf [unpublished].

13. Qureshi, N. R., Hien, T. T., Farrar, J., & Gleeson, F. V. (2006). The radiologic manifestations of H5N1 avian influenza. *Journal of thoracic imaging*, *21*(4), 259–264. https://doi.org/10.1097/01.rti.0000213573.94032.53

14. Zhang, S., Liu, Y., Wang, X., Yang, L., Li, H., Wang, Y., … & Hu, L. (2020). SARS-CoV-2 binds platelet ACE2 to enhance thrombosis in COVID-19. *Journal of hematology & oncology*, *13*(1), 120. https://doi.org/10.1186/s13045-020-00954-7

15. Dhama, K., Khan, S., Tiwari, R., Sircar, S., Bhat, S., Malik, Y. S., … & Rodriguez-Morales, A. J. (2020). Coronavirus Disease 2019-COVID-19. *Clinical microbiology reviews*, *33*(4), e00028-20. https://doi.org/10.1128/CMR.00028-20

Received: 24 Dec 2021
Accepted: 13 Mar 2022