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Screening for and Treatment of Epstein—Barr Virus Infection Reactivation as Rehabilitation Tool in Uncontrolled Asthma Patients Who Have Had COVID-19

Objective — to evaluate the frequency of the reactivation of Epstein—Barr virus (EBV) infection among patients with uncontrolled asthma who have had COVID-19 and to determine its treatment effectiveness as a rehabilitation tool.

Materials and methods. The study included 25 uncontrolled asthma patients with post-COVID syndrome. For all patients, we determined the presence of active EBV infection by polymerase chain reaction of saliva and nasopharyngeal samples. For the treatment of uncontrolled asthma patients with post-COVID syndrome and reactivation of EBV infection acyclovir 400 mg 4 times a day for 20 days, proteflazid 15 drops twice daily for 2 months, decametoxin 0.02 % solution nebulizer therapy for 10 days were prescribed. Before and after the therapy, the patients completed the Asthma Control Test (ACT) and Asthma Control Questionnaire (ACQ-7). In addition, we performed spirometry and the 6-Minute Walk Test (6MWT) to assess the treatment efficacy.

Results and discussion. Reactivation of EBV infection was detected in 19 (76.0 ± 8.5) % of patients with uncontrolled bronchial asthma who have had COVID-19. For these 19 patient we prescribed therapy as listed in materials and methods. Under the treatment, there was a decrease in the severity of respiratory symptoms and an improvement in the control of bronchial asthma symptoms. After two months of treatment, the patients had a statistically significant enhancement in the control of asthma symptoms: ACT increased from (11.8 ± 0.7) to (19.3 ± 0.7) points, ACQ-7 decreased from (2.6 ± 0.1) to (1.1 ± 0.1) points with clinically important and statistical significance ($p < 0.05$). The pulmonary function, namely the vital and forced vital capacity and the bronchial patency (forced expiratory volume in the first second) improved under the study treatment. The small airways obstruction (mid-expiratory flow) decreased with a statistically significant difference. There was a physical exercise tolerance improvement by the 6MWT.

Conclusions. Reactivation of EBV infection is often (76 %) complication of COVID-19. The use of acyclovir, proteflazid and topical decametoxin therapy for these patients allows improving in asthma control according to the ACT and ACQ-7 questionnaires. With the improvement of the pulmonary function test, the exercise tolerance of the patients became better. Screening for and treatment of EBV infection reactivation is a possible rehabilitation element in uncontrolled asthma patients who have had COVID-19.

Keywords

COVID-19, Epstein—Barr virus, rehabilitation, uncontrolled asthma.

The coronavirus disease 2019 (COVID-19) pandemic had a negative impact on the asthmatic patients. The course of bronchial asthma (BA) worsened in people who suffered from COVID-19. Although asthma did not become a factor of the

more severe COVID-19 infection, people with asthma have had COVID-19 like the other population [10].

The severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is notable for causing long-term

complications in many patients. The condition, when the symptoms that occurred during the acute phase of COVID-19 persist for more than 12 weeks, and has no other alternative diagnoses, experts defined as post-COVID syndrome [6]. The overall prevalence of new or persistent symptoms 12 or more weeks after acute SARS-CoV-2 infection is up to 50.9 % in patients with COVID-19, including 58.2 % of patients with severe pneumonia, 36.6 % of patients with mild pneumonia, and 37.0 % of patients without pneumonia in acute period of the disease [14]. The prevalence of post-COVID syndrome among asthma patients is up to 56.0 % [15].

The primary goal of BA patients' treatment is to achieve complete control over symptoms and minimize the future risks of asthma-related mortality, exacerbations, persistent airflow limitation, and adverse effects of therapy. Despite the availability of effective treatments for asthma, asthma control in real life is lower, than expected [7]. There are both general and pandemic-related barriers to achieving the goal of treating BA. In most patients, the causes for the lack of asthma control are incorrect inhaler technique, poor adherence to treatment, overuse of short-acting bronchodilators, comorbidities, the influence of adverse environmental conditions and psychosocial factors [7]. The COVID-19 pandemic has affected the asthma control through quarantine restrictions and the influence of post-acute COVID-19 disorders [1]. On the one hand, quarantine restrictions had a positive effect on the asthma course: there was a decrease in the seasonal respiratory viral infections frequency and the asthma exacerbations number [4]. On the other hand, pandemic significantly affected asthma patients due to a high level of stress, anxiety and limited access to regular medical care [5]. Health disorders in post-COVID-19 period negatively influence the control of BA. After recovery from the acute COVID-19, a large proportion of asthma patients experienced poorer control and need for increased asthma maintenance therapy [13].

COVID-19 predisposes patients to secondary viral, bacterial and other infections. Epstein–Barr virus (EBV) infection reactivation is one of them and the part of the pathogenesis mechanisms of post-COVID syndrome. This complication occurs in two-thirds of people who undergo long-term consequences of COVID-19 [16].

The symptoms of post-COVID syndrome (fatigue, dyspnea, cough, sore throat, brain fog, dizziness, loss of attention, confusion, myalgia, arthralgia, chest pain, tachycardia, palpitations, anxiety, depression, insomnia), significantly deteriorate the daily activity, ability to work and quality of life of the patients [6]. The signs of EBV infection reactivation are similar: poor concentration, sleep disturbance,

musculoskeletal pain, pharyngitis and severe fatigue, brain fog, headaches [16]. That is why people with such disorders need rehabilitation. The actual questions are how often the asthma patients has EBV infection reactivation after COVID-19, can EBV reactivation lead to loss of the asthma control in BA patients and how the treatment of this complication can influence asthma control.

Objective — to evaluate the frequency of the reactivation of Epstein–Barr virus infection among patients with uncontrolled asthma who have had COVID-19 and to determine its treatment effectiveness as rehabilitation tool.

Materials and methods

To select the patients for the study, we examined 132 patients who received hospital treatment due to post-COVID syndrome at the SO «National Scientific Center of Phthisiatry, Pulmonology and Allergology named after F.G. Yanovskyi NAMS of Ukraine».

Compliance with ethical requirements. The study carried out in accordance with the standards set forth in the Helsinki Declaration of the World Medical Association «Ethical principles for conducting scientific medical research involving human subjects». The study was approved with the local Medical Ethics Committee of the Center. Participants (or their legal representatives) familiarized themselves with the study protocol and signed an informed consent form to participate in the study.

The inclusion criteria for the study were:

- 1) men or women over the age of 18 years;
- 2) the diagnosed uncontrolled BA despite adequate maintenance therapy;
- 3) COVID-19 in the anamnesis according to the criteria defined in the Order of the Ministry of Health of Ukraine «Clinical management of patients with COVID-19: clinical guidelines».

The exclusion criteria were:

- 1) the presence of other serious diseases (tuberculosis, malignancy, AIDS, etc.), which significantly affect patient's condition, clinical parameters, treatment and may affect the analysis and interpretation of the results;
- 2) contraindications to the use of antiviral medicines;
- 3) refusal of patients to carry out additional methods of examination, as well as refusal of the patient to participate in scientific clinical research.

For all patients we determined the presence of active EBV infection by polymerase chain reaction of saliva and nasopharyngeal samples.

For the treatment of uncontrolled asthma patients with post-COVID syndrome and reactivation of EBV infection, we proposed the following scheme: acyclovir 400 mg 4 times a day for 20 days, proteflazid 15 drops twice daily for 2 months. As EBV

persists not only in human B cells, but also in the oropharyngeal epithelial cells [17], we prescribed the additional topical treatment with the decamethoxin 0.02 % solution nebulizer therapy twice daily for 10 days. All patients continued their maintenance and rescue asthma treatment according to current guidelines [7].

Before and after two months from the start of therapy the patients completed Asthma Control Test (ACT) and Asthma Control Questionnaire (ACQ-7) [11]. In addition, we performed spirometry to assess the treatment efficacy. We evaluated the following spirometry parameters: the vital capacity (VC), forced expiratory volume in the first second (FEV₁), forced vital capacity (FVC), maximal expiratory flow (MEF₇₅, MEF₅₀ and MEF₂₅), the flows where 75 %, half or 25 % of forced vital capacity remains to be exhaled. All data are presented as percentages of predicted values [9]. The patients underwent the 6-Minute Walking Test (6MWT) to analyze the hypoxemia and functional performance capacity [12].

Data collection and statistical analysis were carried out using licensed software products, Microsoft Office Professional and MS Excel, with mathematical and statistical functions. The studied data were evaluated by determining the mean (M) and its standard error (m). To compare the parameters the paired samples t-test used [22]. The critical level of significance when testing statistical hypotheses was set at 0.05.

Results and discussion

According to the inclusion and exclusion criteria, 25 patients (12 men and 13 women, average age 50.3 ± 3.1 years) with uncontrolled asthma who have had COVID-19 and had clinical signs of post-COVID syndrome were selected for further investigation. They received patient education, checked the inhalation technique and corrected maintenance treatment (inhaled corticosteroids plus long-acting β_2 -agonists controller and reliever) for at least 4 weeks before the study started. The characteristic of the participants are shown in Table 1.

The study population had tendency to have excessive body weight or to be obese. Smoking status in the study group is presented in Figure. The mean smoking experience among current and ex-smokers was (16.0 ± 7.3) pack-years.

All of these 25 patients, who failed to achieve asthma control with standard therapy, were screened for reactivation of EBV infection. According to the polymerase chain reaction laboratory results, reactivation of chronic EBV infection was detected in 19 (76.0 ± 8.5) % of patients with uncontrolled BA who have had COVID-19. For these 19 patient

Table 1. The characteristic of the participants

Characteristics	Diapason min—max	Mean $\pm$ mean error
Age, years	18–72	50.3 ± 3.1
Height, cm	156–200	172.9 ± 2.4
Weight, kg	65–113	87.5 ± 3.1
Body mass index, kg/m ²	18.6–39.1	29.4 ± 1.1
ACT, points	6.0–19.0	11.2 ± 0.7
ACQ, points	1.14–4.43	2.7 ± 0.1
VC, %	51.7–121.8	84.3 ± 3.9
FVC, %	50.6–127.7	85.3 ± 4.0
FEV ₁ , %	38.4–114.8	69.1 ± 3.8
FEV ₁ /FVC, %	48.7–91.7	67.4 ± 2.3
MEF ₇₅ , %	19.1–94.0	52.6 ± 4.2
MEF ₅₀ , %	14.3–89.9	39.4 ± 4.0
MEF ₂₅ , %	11.5–83.2	33.6 ± 3.8

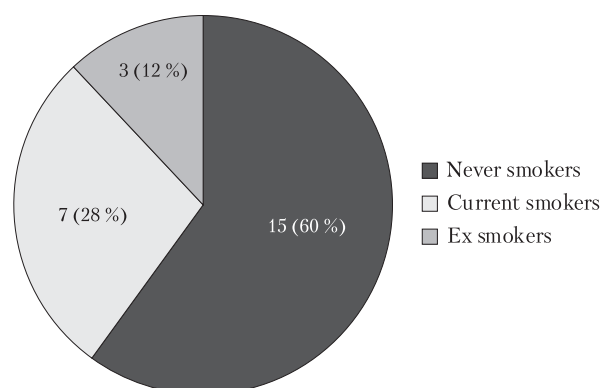


Figure. Smoking status of studied patients

we prescribed acyclovir, proteflazid and nebulizer decamethoxin therapy as listed in materials and methods.

As a result, it was found that during the treatment there was a decrease in the severity of respiratory symptoms and an improvement in the control of BA symptoms (Table 2). After two months of treatment, the patients had a statistically significant enhancement in the control of asthma symptoms: ACT increased from (11.8 ± 0.7) to (19.3 ± 0.7) points, ACQ-7 decreased from (2.6 ± 0.1) to (1.1 ± 0.1) points with statistical significance, $p < 0.05$. These results are also clinically significant because the minimum clinically important difference for the ACT score is 3 points, and for the ACQ-7 — 0.5 points [3].

The pulmonary function also improved under the study treatment. Most parameters of spirometry have positively changed, namely the vital and forced vital capacity of the lungs and the bronchial patency (FEV₁, MEF₇₅). Small airways obstruction decreased, as indicated by MEF₅₀ and MEF₂₅, with

Table 2. Asthma control and spirometry dynamics before and after treatment ($M \pm m$)

Parameters	Before treatment	After treatment	P
ACT, points	11.8 $\pm$ 0.7	19.3 $\pm$ 0.7	0.001**
ACQ, points	2.6 $\pm$ 0.1	1.2 $\pm$ 0.1	0.001**
VC, %	79.2 $\pm$ 3.9	90.4 $\pm$ 4.1	0.001*
FVC, %	79.8 $\pm$ 3.9	92.0 $\pm$ 4.2	0.001*
FEV ₁ , %	64.4 $\pm$ 3.8	78.1 $\pm$ 3.7	0.001*
FEV ₁ /FVC, %	67.5 $\pm$ 2.8	71.1 $\pm$ 3.0	0.056
MEF ₇₅ , %	49.9 $\pm$ 4.6	63.3 $\pm$ 4.9	0.001*
MEF ₅₀ , %	38.2 $\pm$ 4.5	56.0 $\pm$ 5.4	0.001*
MEF ₂₅ , %	30.8 $\pm$ 3.5	41.9 $\pm$ 5.2	0.001*

Note. * Statistically significant difference before and after treatment, $p < 0.05$; * clinically important difference before and after treatment.

Table 3. 6MWT dynamics before and after treatment ($M \pm m$)

Parameters	Before treatment	After treatment	P
Borg Dyspnea Scale before test, points	2.3 $\pm$ 0.2	2.2 $\pm$ 0.1	0.083
SpO ₂ before test, %	97.7 $\pm$ 0.2	97.9 $\pm$ 0.2	0.215
Walking distance, m	383.6 $\pm$ 19.6	392.1 $\pm$ 17.8	0.085
Borg Dyspnea Scale after test, points	3.9 $\pm$ 0.2	3.6 $\pm$ 0.2	0.015*
SpO ₂ after test, %	95.9 $\pm$ 0.2	96.5 $\pm$ 0.2	0.007*

Note. * Statistically significant difference before and after treatment, $p < 0.05$.

a statistically significant difference ($p < 0.05$). At the same time due to symptoms reduction, and the lung function enhancement, there was a physical exercise tolerance improvement in all parameters by the 6MWT (Table 3). So the breathlessness after the test decreased from (3.9 $\pm$ 0.2) to (3.6 $\pm$ 0.2) points with a statistically significant difference, $p < 0.05$. SpO₂ also improved significantly after the test (95.9 $\pm$ 0.2) to (96.5 $\pm$ 0.2) %, $p < 0.05$.

With proper treatment of BA, patients have the opportunity to feel good, to work, and to perform family and social activities. In the treatment of BA, it is necessary and worthwhile to achieve the goal of the best possible results for the patient. Despite the availability of effective treatment options the definite part of the patients is out of asthma control [7]. The burden of uncontrolled asthma causes economic losses at the level of 15 billion dollars per year in the United States. Unfortunately, uncontrolled asthma can cause disability [21]. The problem of disability due to uncontrolled asthma has become more complex due to the impact of the consequences of the COVID-19 pandemic. Moreover, the long-COVID itself is a condition that causes loss of

working capacity [19]. Of course, patients with disabilities need recovery and rehabilitation either in asthma or in long-COVID and more in both.

COVID-19 negatively affects the functions of many organs and systems of the body. Because of the adverse impact on immunity, patients have reactivation of chronic latent infections, which dramatically worsens the status of patients with concomitant asthma. In literature data, the EBV infection reactivation takes place in 66.7 % patients with post-COVID syndrome [8]. On another trial, the frequency of EBV reactivation was 42.6 % whereas EBV plus type 6 herpes virus reactivation found in 32.4 % of these post-COVID patients [23]. This data corresponds with our study, where the frequency of reactivation of chronic EBV infection is 76.0 % among asthma patients. We did not find other data regarding EBV reactivation in the BA patient population.

The essence of rehabilitation in medicine is to optimize functioning and reduce disability in individuals with health conditions [18]. Clinicians recognized the importance of multidisciplinary rehabilitation for post-COVID patients since the beginning of the pandemic, but detailed guidelines for rehabilitation procedures and resources have taken some time to develop [20].

Both in uncontrolled asthma and in post-COVID syndrome alternative diagnosis should be excluded [6, 7]. So screening for EBV infection reactivation is useful for clarifying the cause of both conditions. Treatment of EBV infection reactivation is a complex challenge. The fact is that most antiviral drugs suppress the replication of EBV *in vitro*, but have not demonstrated clinical efficacy. The most effective drug with the best safety profile for the treatment of EBV is acyclovir, which inhibits virus replication in the nasopharynx. The problem of such therapy is the resumption of viral shedding after drug withdrawal due to immunological reasons [2]. That is why, in our study, we additionally to acyclovir used not only proteflazid for the purpose of immunocorrection, but also local therapy of the nasopharynx to reduce the degree of local inflammation and inhibit virus replication.

EBV exacerbation treatment improved clinical and functional health signs in patients with BA. This, in turn, improved the physical exercise tolerance, which was objectively reflected in the 6-minute walking test. Improvement in the functional status evidences the achievement of a rehabilitation effect in the patients.

Prospects for further research. The perspective of further research is to investigate the role of other secondary infection complications after acute COVID-19 in asthma control deterioration and to

to develop algorithms for the rehabilitation of uncontrolled asthma patients with post-COVID syndrome.

Conclusions

In (76.0 ± 8.5) % of the patients with uncontrolled asthma who have had COVID-19, reactivation of chronic EBV infection took place.

The use of acyclovir, proteflazid and topical decamethoxin therapy for these patients allows improve-

ment in asthma control according to the ACT and ACQ-7 questionnaires.

With the improvement of the pulmonary function test, the exercise tolerance of the patients became better.

Screening for and treatment of EBV infection reactivation is a possible rehabilitation element in uncontrolled asthma patients who have had COVID-19.

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Скринінг та лікування реактивації Епштейна—Барр вірусної інфекції як елемент реабілітації в пацієнтів із неконтрольованою бронхіальною астмою, які перенесли COVID-19

Мета роботи — оцінити частоту реактивації Епштейна—Барр вірусної (ЕБВ) інфекції в пацієнтів із неконтрольованою бронхіальною астмою, які перенесли коронавірусну хворобу-2019 (COVID-19), та визначити ефективність її лікування як засобу реабілітації.

Матеріали та методи. У дослідженні взяли участь 25 пацієнтів із неконтрольованою астмою та постковідним синдромом. У всіх пацієнтів методом полімеразної ланцюгової реакції в зразках слини та мазках із носоглотки визначали наявність активної ЕБВ-інфекції. Для лікування хворих на неконтрольовану астму з постковідним синдромом та реактивацією ЕБВ-інфекції призначали ацикловір по 400 мг 4 рази на добу впродовж 20 днів, протеклазид по 15 крапель двічі на добу впродовж 2 міс, декаметоксин 0,02 % розчин для небулайзерної терапії впродовж 10 днів. До і після терапії пацієнти заповнювали астма-контрольний тест (АКТ) і анкету контролю астми (АСQ-7). Крім того, проведено спірометрію та тест із 6-хвилинною ходьбою для оцінки ефективності лікування.

Результати та обговорення. У 19 (76,0 ± 8,5) % хворих на неконтрольовану бронхіальну астму, які перенесли COVID-19, виявлено реактивацію хронічної ЕБВ-інфекції. Цим хворим призначено терапію ацикловіром, протеклазидом та декаметоксином. Під час лікування відзначено зменшення респіраторних симптомів і поліпшення контролю симптомів БА. Через 2 міс лікування в пацієнтів зафіксували статистично значуще поліпшення контролю симптомів астми: результат АКТ підвищився з (11,8 ± 0,7) до (19,3 ± 0,7) бала, оцінка за АСQ-7 зменшилася з (2,6 ± 0,1) до (1,1 ± 0,1) бала ($p < 0,05$). Функція легень, а саме життєва та форсована життєва ємність, а також бронхіальна прохідність (об'єм форсованого видиху за першу секунду) поліпшилися. Обструкція малих дихальних шляхів (середні експіраторні потоки) статистично значучо зменшилася. Зафіксовано поліпшення толерантності до фізичних навантажень за всіма параметрами тесту з 6-хвилинною ходьбою.

Висновки. У (76,0 ± 8,5) % пацієнтів із неконтрольованою БА, які перенесли COVID-19, виявлено реактивацію хронічної ЕБВ-інфекції. Застосування ацикловіру, протеклазиду та місцевої терапії декаметоксином дає змогу поліпшити контроль бронхіальної астми в цих пацієнтів. З поліпшенням показників функції легень збільшилася толерантність до фізичних навантажень. Скринінг та лікування реактивації ЕБВ-інфекції є можливими методами реабілітації пацієнтів із неконтрольованою бронхіальною астмою, які перенесли COVID-19.

Ключові слова: COVID-19, Епштейна—Барр вірус, реабілітація, неконтрольована астма.

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