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LEIDEN MUTATION (RS6025) IN A SEVERE COVID-19 PNEUMONIA PATIENT WITH DOWN SYNDROME: A CLINICAL CASE

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Key words: *clinical case, COVID-19, Down syndrome, pneumonia, Leiden mutation, rs6025*
Ключові слова: *клінічний випадок, COVID-19, синдром Дауна, пневмонія, Лейденська мутація, rs6025*

Abstract. Leiden mutation (rs6025) in a severe COVID-19 pneumonia patient with Down syndrome: a clinical case. Pokhylko V.I., Cherniavska Y.I., Fishchuk L.Y., Rossokha Z.I., Ievseienkova O.G., Dubitska O.M., Popova O.F., Fastovets M.M., Kaliuzhka O.O., Gorovenko N.G. *COVID-19 was first reported in December 2019 in Wuhan (Hubei Province, China). Later, the pandemic of this disease took the world by storm, challenging the medical community. Its*

clinical manifestations vary from asymptomatic to a severe course that requires hospitalization and intensive therapy with oxygen support. The mortality rate in patients with a severe course of COVID-19 can exceed 50% The majority of fatal cases of COVID-19 were associated with thrombotic events, despite the prophylactic use of anticoagulant therapy. Numerous theoretical overviews and research articles indicate the need for genetic testing in patients with COVID-19 to determine the genetic profile of proteins involved in thrombophilia. According to the researchers, the Leiden mutation (G1691A, rs6025) of the FV gene is one of the promising candidates for testing. The aim of the work was to demonstrate the clinical features of the severe course of COVID-19 in the presence of the Leiden mutation. 58 patients with COVID-19 of the intensive care unit were genotyped. The Leiden mutation in the heterozygous state was found only in one patient, who had Down syndrome. The Leiden mutation was detected with a frequency of 1.72% in the investigated group. The described clinical case clearly showed that individuals with Down syndrome, associated with hereditary thrombophilia are at risk of undesirable clinical consequences in the treatment of COVID-19. The condition of the patient with the Leiden mutation was severe when admitted to the hospital. The score according to the sequential organ failure assessment scale was 2 points. Bilateral multisegmental pneumonia was detected on the X-ray. On the second day after admission, due to the development of acute respiratory distress syndrome and multiple organ failure, the patient was transferred to the intensive care unit, where he received oxygen therapy through a facial mask. Medical treatment was carried out according to the protocol: non-steroidal anti-inflammatory drugs, antibacterial therapy, anticoagulants, sympathomimetics, and glucocorticosteroids. Despite the medical measures taken, progression of respiratory failure, renal failure, and portal hypertension was noted. On the 11th day, the patient developed asystole. Resuscitation measures were unsuccessful. Thus, the described case of a severe course of COVID-19 in a carrier of a heterozygous variant of the Leiden mutation with Down syndrome confirms the recommendations regarding the need for genetic testing for thrombophilia in high-risk groups and the appointment of personalized measures to prevent complications.

Реферат. Лейденська мутація (rs6025) у пацієнта із тяжким перебігом пневмонії COVID-19 та синдромом Дауна: клінічний випадок. Похилько В.І., Чернявська Ю.І., Фіщук Л.Є., Россоха З.І., Євсеєнкова О.Г., Дубіцька О.М., Попова О.Ф., Фастовець М.М., Калюжка О.О., Горовенко Н.Г. *Уперше про COVID-19 було повідомлено в грудні 2019 року в Ухані (провінція Хубей, Китай). Пізніше пандемія цього захворювання захопила весь світ, кинувши виклик медичній спільноті. Його клінічні прояви варіюють від безсимптомного до тяжкого перебігу, що потребує госпіталізації та інтенсивної терапії із кисневою підтримкою. Рівень смертності пацієнтів із тяжким перебігом COVID-19 може перевищувати 50%. Більшість летальних випадків COVID-19 були пов'язані з тромботичними подіями, незважаючи на профілактичне застосування антикоагулянтної терапії. Численні теоретичні огляди та дослідницькі статті вказують на необхідність генетичного тестування пацієнтів із COVID-19 для визначення генетичного профілю білків, залучених до тромбофілії. На думку дослідників, Лейденська мутація (G1691A, rs6025) гена FV є одним з перспективних кандидатів для тестування. Мета роботи – на прикладі клінічного випадку продемонструвати клінічні особливості тяжкого перебігу COVID-19 за наявності Лейденської мутації. Було генотиповано 58 пацієнтів з COVID-19 відділення інтенсивної терапії. Лейденська мутація в гетерозиготному стані була виявлена лише в одного, який мав синдром Дауна. Лейденська мутація була виявлена нами в групі обстежених з частотою 1,72%. Описаний нами клінічний випадок наочно показав, що особи із синдромом Дауна, поєднаним зі спадковою тромбофілією, є в групі ризику небажаних клінічних наслідків при лікуванні COVID-19. При надходженні на стаціонарне лікування стан пацієнта з Лейденською мутацією був тяжким. Оцінка за шкалою динамічної оцінки органної недостатності становила 2 бали. На рентгенограмі було виявлено двобічну полісегментарну пневмонію. На другу добу після надходження пацієнта у зв'язку з розвитком гострого респіраторного дистрес-синдрому та поліорганної недостатності було переведено у відділення анестезіології та інтенсивної терапії, де він отримував кисень через лицеву маску. Проводилося медикаментозне лікування згідно з протоколом: нестероїдні протизапальні препарати, антибактеріальна терапія, антикоагулянти, симпатоміметики та глюкокортикостероїди. Незважаючи на проведені лікувальні заходи, відмічалося прогресування дихальної недостатності, ниркової недостатності та портальної гіпертензії. На 11 добу у хворого виникла асистолія. Реанімаційні заходи успіху не мали. Отже, описаний випадок тяжкого перебігу COVID-19 у носія гетерозиготного варіанту Лейденської мутації з синдромом Дауна підтверджує рекомендації щодо необхідності генетичного тестування на тромбофілію у групах підвищеного ризику та призначення персоналізованих заходів щодо профілактики ускладнень.*

COVID-19 is an infectious disease caused by the SARS-CoV-2 virus. Clinical manifestations of this disease vary from asymptomatic to a severe course that requires hospitalization and intensive therapy with oxygen support. The mortality rate in patients with a severe course of COVID-19 can exceed 50% [1]. According to the presented histopathological results of autopsies in patients infected with SARS-CoV-2, microthrombi were found in 60% of autopsies, and in 93% of these cases – precisely in the lungs [2]. Moreover, studies have confirmed that the majority of fatal cases of COVID-19 were associated with pulmonary embolism, despite the prophylactic use of anticoagulant therapy [3]. Therefore, the improvement of diagnostic and treatment strategies aimed at reducing thrombotic complications in this disease is extremely relevant.

Numerous theoretical overviews and research articles indicate the need for genetic testing in patients with COVID-19 to determine the genetic profile of proteins involved in thrombophilia [3-9]. This is due to the fact that the carrier of hereditary thrombophilia gene variants has been associated with a complicated course and mortality in patients with COVID-19. This is especially true for high-risk groups – individuals who, which according to scientific literature, are more likely to carry mutations in the genes of hereditary thrombophilia – persons with Down's syndrome, and those who have a history of cardiovascular diseases, reproductive losses, poor response to therapy with antithrombotic drugs, etc [10, 11, 12, 13, 14].

In our previous study, we have already examined genetic factors, that influenced the course and mortality of COVID-19 [15]. According to this research design, patients were genotyped for the well-known genetic markers of thrombophilia – *F2* (G20210A, NM_000506.5(F2):c.*97G>A, rs1799963), *FV* (G1691A, NM_000130.4(F5):c.1601G>A (p.Arg534Gln), rs6025) and *MTHFR* (C677T, NM_005957.5(MTHFR):c.665C>T (p.Ala222Val), rs1801133; A1298C, NC_000017.11:g.69928988T>C, rs180113) [14, 16, 17]. Out of the total 58 patients, who received treatment in the intensive care unit of the municipal enterprise "Poltava Regional Clinical Infectious Disease Hospital of the Poltava Regional Council" with a diagnosis of viral COVID-19 pneumonia, 22 patients died. Fifty patients (86%) had a history of comorbidities, such as cardiovascular disease, cancer, tuberculosis, and type II diabetes. In one (1.72%) of 58 patients, the Leiden mutation was detected in a heterozygous state – genotype GA for the G1691A variant of the *FV* gene.

The research was conducted in accordance with the World Medical Association Declaration of Helsinki and was approved by the Commission on Bioethics of the Poltava State Medical University (protocol No. 218 as of August 23, 2023). Patients were included in the study after signing the informed consent form. In addition, written informed consent was obtained from the patient's immediate family members for the publication of this case report and any accompanying images. The case report has been completely anonymized to protect patient confidentiality.

The aim of the work was to demonstrate the clinical features of the severe course of COVID-19 in the presence of the Leiden mutation.

MATERIALS AND METHODS OF RESEARCH

All included in study patients underwent standard daily repeated clinical, instrumental and laboratory examinations. The Glasgow coma scale and the number of points on the SOFA scale were evaluated. The SpO_2/FiO_2 ratio was analyzed to assess the severity of respiratory disorders due to the inability to perform the PaO_2 study. According to the recommendations of the Ministry of Public Health of Ukraine, if the SpO_2/FiO_2 index is less than 315 – it is regarded as acute respiratory distress syndrome [18]. Instrumental screening methods were used for all patients to confirm the diagnosis of viral pneumonia: computed tomography of the lungs or X-ray examination.

For molecular genetic testing, DNA was isolated from peripheral blood using the commercial kit "Quick-DNA Miniprep Plus Kit" ("Zymo Research") according to the manufacturer's instructions. Molecular genetic studies of variants of genes *F2* (rs1799963), *FV* (rs6025) and *MTHFR* (rs1801133, rs180113) were carried out using the polymerase chain reaction-restriction fragment length polymorphism method according to previously published protocols [19, 20]. The studied gene regions were amplified using the commercial kit "Dream Taq Green PCR Master Mix" ("ThermoScientific") and specific oligonucleotide primers ("Metabion"). Following digestion with suitable restriction enzymes ("ThermoScientific"), fragments were separated using agarose gel electrophoresis and visualized on a UV transilluminator

RESULTS AND DISCUSSION

In April 2021, a 43-year-old male patient with Down syndrome (the diagnosis was established on the first year of life), type II diabetes, diabetic nephropathy, congenital atrial septal defect, not vaccinated against COVID-19, was admitted with complaints of headache, general weakness, and high fever up to 38.5°C, which persisted despite the use of antipyretics.

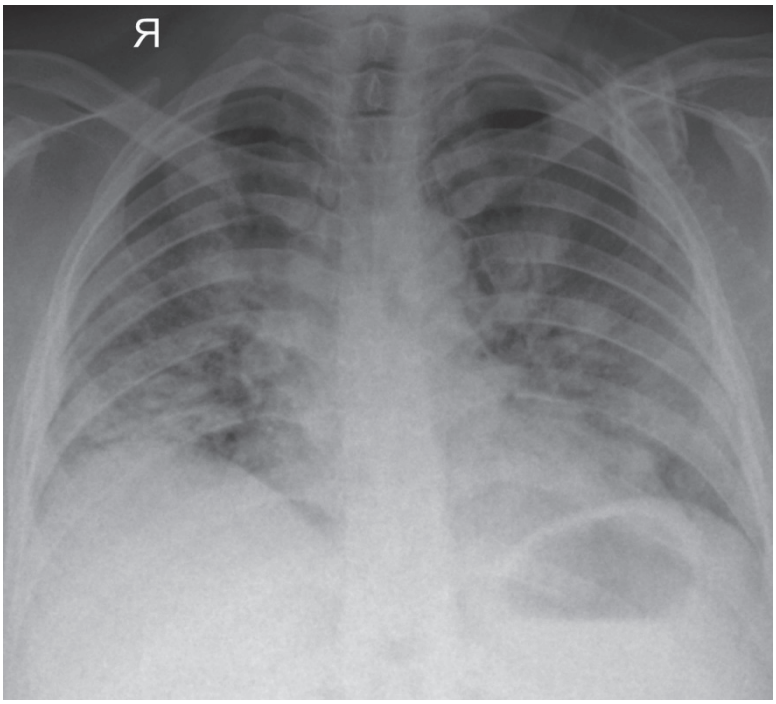
Upon admission, the general condition of this patient was severe due to pronounced microcirculatory disorders, arterial hypotension, tachypnea, edematous syndrome, hepatomegaly, portal hypertension syndrome, ascites, and decreased urine output rate. The patient was conscious. Meningeal, focal neurological signs were not detected. Tendon reflexes and muscle tone were within normal ranges. During hospitalization, the body temperature was 37.7-37.2°C. The patient presented with skin pallor, pastiness, and swelling of the lower extremities. There was tachypnea of a mixed origin, with involvement of pliable areas of the chest, breathing rate – 22-24 per minute, SpO_2 – 92-96% (on room air), jugular venous pressure was normal – 6 cmH_2O. On auscultation – moist rales of various calibers on both sides, coarse systolic murmur in the II-IIIrd intercostal space on the left, and muffled heart sounds. Heart rate – 72-75 per minute, blood pressure – 105/70, 90/60 mmHg. The abdomen was enlarged due to ascites, and the liver was +4.0 cm from the edge of the costal arch, dense

on palpation. No irritation of the peritoneum was detected. There was no vomiting, and appetite sharply was reduced. The stool was without pathological impurities. The urine output was decreased – 300-400 ml/24 h. According to the sequential organ failure assessment scale, the severity of multiple organ failure was 2 points.

We examined the patient for thrombophilia genes, and the obtained results revealed the presence of a heterozygous GA genotype of the *FV* gene. No mutations in the *FII* gene were found (GG genotype). In addition, TT and AA genotypes according to the C677T and A1298C variants of the *MTHFR* gene were detected.

In the complete blood count, there was an increase in erythrocyte sedimentation rate to 17-27 mm/h, a shift of leucogram to the left: stab neutrophils – 45-22%, segmented – 50-67%, hemoglobin – 18.0-16.3 g/dl, erythrocytes – 5.5-5.96 $*10^{12}$/l. Through the clotting studies, we detected, on the one hand, an increase in the level of fibrinogen up to 8.1 g/l (tendency to hypercoagulation), but also an increase in active partial thromboplastin time to 57 sec and prothrombin time to 20-22 sec (hypocoagulation changes), which may be a sign of DIC syndrome onset as one of the components of multiple organ failure. Blood glucose was 6.4-11.2 mmol/l. Polymerase chain reaction test for COVID-19 was positive on admission, on the 3rd and 7th day of hospitalization.

Bilateral multisegmental pneumonia was detected on the X-ray (Fig.). An ultrasound scan confirmed congenital atrial septal defect, liver cirrhosis, diabetic nephropathy, and reactive changes in the pancreas. During esophagogastroduodenoscopy, it was found that 3 bluish veins with a diameter of 0.4 – 0.5 cm protruded into the lumen of the esophagus, starting from the 2nd narrowing with a transition to the cardiac part of the stomach.



Chest X-ray of the patient, bilateral pulmonary infiltrates

The patient was transferred to the intensive care unit on the 2nd day after admission and received oxygen through a dense facial mask. He received the following pharmacological treatment – NSAIDs (paracetamol 10-30 mg/kg/d), antibacterial therapy (ceftriaxone, amikacin), anticoagulants (heparin 100 Units/kg/d), sympathomimetics in extremely high doses – norepinephrine 0.5-2 μg/kg/min, glucocorticosteroids – dexamethasone 6 mg/day for 11 days.

Regardless of the treatment measures taken in this case, there was a progression of respiratory failure – an increase in oxygen dependence (FiO_2 – 100%, PaO_2/FiO_2 ratio – 80, signs of acute respiratory distress syndrome), renal failure (edema, oligo-anuria), and portal hypertension. On the 11th day, the patient developed asystole. Resuscitation was unsuccessful.

Final clinical diagnosis: acute respiratory disease COVID-19, confirmed case, bilateral multisegmental pneumonia, respiratory failure of 2nd grade, Down syndrome, congenital atrial septal defect, type II diabetes, diabetic nephropathy, cirrhosis, portal hypertension, multiple organ failure.

The point mutation G1691A of the *FV* gene leads to the substitution of arginine (Arg, R) in codon 506 for glutamine (Gln, Q), resulting in resistance to the action of activated protein C (APC) [21]. It was experimentally confirmed that purified Gln506-FVa is not completely resistant to APC and suggested that the variant Gln506-FVa is approximately 10-fold less sensitive to APC than the normal FVa [22]. Subsequently, the lack of inactivation of Gln506-FVa by APC leads to a 5-10-fold increase in the probability of blood clot formation [23]. Studies demonstrated associations of the G1691A variant of the *FV* gene with an increased risk of deep vein thrombosis, coronary artery disease, recurrent pregnancy loss in women, preeclampsia in pregnant women, and neonatal hypoxic-ischemic encephalopathy [24, 25, 26, 27].

As for COVID-19, the study by Lapić et al. found no effect of the G1691A variant of the *FV* gene on the disease severity in patients with COVID-19 [8]. On the other hand, Stevens et al. proved that the presence of the G1691A variant of the *FV* gene is associated with an increased risk of venous thromboembolism associated with COVID-19 [7]. In turn, the presence of venous thromboembolism in patients with COVID-19 was associated with an increased risk of lethal outcome [7]. The results of the large cohort study by Kiraz et al. also indicate an association of carriage of the Leiden mutation with an increased risk of complications/lethality of COVID-19 [4]. There are also data indicating that patients with Leiden mutation produce higher levels of soluble fibrin, which may serve as a cofactor in tissue plasminogen activator-induced plasminogen activation, leading to a more sustained activation of fibrinolysis with the higher fibrinogen and fibrin-degradation products output [28]. In our patient we also detected an increase in the level of fibrinogen. Applying the analyzed data, we can predict that patients with COVID-19 in whom the G1691A variant of the *FV* gene was detected (in a homo- or heterozygous condition), have a tendency to thrombosis. Consequently, such patients most likely will benefit more from higher doses of antithrombotic drugs. In addition, taking into account the presence of the TT genotype of the *MTHFR* gene, it may be appropriate to prescribe vitamin B12 and folic acid to such patients [29]. However, the economic feasibility of conducting genetic testing in all patients with COVID-19 should also be taken into account in this context. Thus, the rate of the GA genotype according to the G1691A variant of the *FV* gene for the population of Ukraine is 3.5% [30]. Therefore, it is advisable to carry out genetic testing for thrombophilia, in particular the G1691A variant of the *FV* gene, in high-risk groups – those who have a history of cardiovascular diseases, reproductive losses, chromosomal pathology, poor response to therapy with antithrombotic drugs, etc.

Summarizing the above, as a result of testing 58 patients with severe COVID-19-associated pneumonia, the Leiden mutation was detected with a frequency of 1.72%, which did not exceed the population rate [30]. At the same time, the Leiden mutation was detected in a person with the chromosomal pathology – Down syndrome. In the large multicenter studies, people with Down syndrome were found to be more prone to a complicated course of COVID-19 [31, 32]. The results of previous studies demonstrate the dysregulation of the immune system among individuals with Down syndrome, which in turn leads to an increased cytokine storm and thus may be associated with a higher thrombotic risk [33, 34]. But, in our opinion, this may have another explanation. We assume that another reason for the complicated course of COVID-19 in persons with Down syndrome, in particular, thromboembolic complications, is the carriage of mutations in the genes of hereditary thrombophilia, and our clinical case is only a confirmation of this. Therefore, this clinical case clearly shows that individuals with Down syndrome who have hereditary thrombophilia are at risk of adverse clinical consequences during the treatment of COVID-19.

CONCLUSION

1. The course of severe COVID-19 associated pneumonia in a person with Down syndrome and Leiden mutation was accompanied by the development of thrombophilic disorders, despite the standard therapy.
2. For patients with COVID-19 from high-risk groups, in particular, individuals with Down syndrome, genetic testing for thrombophilia may be recommended for timely personalized optimization of therapy with antithrombotic drugs.

Contributors:

Pokhylko V.I. – writing – original draft, project administration;

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Fastovets M.M. – resources;

Kaliuzhka O.O. – supervision, software;

Gorovenko N.G. – project administration, conceptualization.

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