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COAGULATION AND ANTICOAGULATION PARAMETERS IN MULTIPLE SCLEROSIS PATIENTS WITH AND WITHOUT COVID-19

Tetiana I. Halenova[1], Nataliia G. Raksha[1], Tetiana B. Vovk[1], Vitalii L. Karbovskyy[2], Svitlana M. Sholomon[3], Volodymyr S. Melnyk[3], Olexii M. Savchuk[1]

1 – Taras Shevchenko National University of Kyiv, Kyiv, Ukraine
2 – Limited liability company Biopharma-Plasma, Bila Tserkva, Kyiv region, Ukraine
3 – Bogomolets National Medical University, Kyiv, Ukraine

Summary

The aim. To investigate plasma levels of main coagulation and fibrinolytic factors in MS patients with and without COVID-19 history.
Materials and methods. A total of 127 participants were enrolled in this study, including 97 MS patients and 30 healthy controls (HC). Patients with MS were divided into two groups: MS+Covid group (n=41) – patients with MS, who had a laboratory-verified diagnosis of COVID-19 in the past 3-6-month period and MS group (n=56) – patients with MS, who did not suffer from COVID-19 previously. Determination of plasma levels of prothrombin, plasminogen, tissue-type plasminogen activator (tPA), plasminogen activator inhibitor-1 (PAI-1), protein C (PC), soluble thrombomodulin (TM) was performed by means of enzyme-linked immunosorbent assay. Spectrophotometric techniques were used to determine concentrations of fibrinogen, soluble fibrin monomeric complexes (SFMC) as well as plasminogen activity and inhibitory potential of α-2-antiplasmin.
Results. The MS group was characterized by elevated levels of plasma prothrombin, fibrinogen, D-dimer, SFMC, soluble TM compared to HC, while PC concentration did not differ between MS and HC groups. Plasma plasminogen level as well as plasma level of the potential plasmin activity were significantly decreased in MS patients compared to HC group. The plasma tPA level was significantly reduced while plasma PAI-I level was significantly increased in MS patients compared to HC. Patients of MS group had an increased level of plasma α-2-antiplasmin activity compared with HC group. To note, most of studied parameters did not differ between two MS groups, except protein C, soluble thrombomodulin levels and plasma α-2-antiplasmin activity.
Conclusions. The results of our study showed that MS patients have got altered hemostasis parameters; however, further study is necessary to find out the relationship between particular components of coagulation and fibrinolytic systems and pathophysiology of MS. Additionally, our findings demonstrated that a SARS-CoV-2 infection had a limited effect on hemostasis parameters in MS patients, causing changes in only a few parameters, including thrombomodulin and protein C levels as well as α-2-antiplasmin activity.

Keywords: **multiple sclerosis, SARS-CoV-2 infection, hemostasis factors, coagulation, fibrinolysis**

INTRODUCTION

A novel coronavirus named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is an extremely contagious and pathogenic viral agent that appeared at the end of 2019, but in a few months, it spread out all over the world and triggered a pandemic of acute respiratory disease, known as coronavirus disease 2019 (COVID-19) [14]. Although, COVID-19 primarily affects the respiratory system, the findings of current studies have revealed that almost every organ in the body can be injured. Most of pathophysiological effects coursed by SARS-CoV-2 have been attributed to a hyperinflammatory syndrome [15], however, the exact molecular mechanisms behind this viral infection have not been identified yet. The 'cytokine storm' is

suggested to play a crucial role in the immunopathology of COVID-19 and is a key factor affecting disease severity and mortality [2, 27]. The overproduction of pro-inflammatory cytokines, such as interleukin 1β (IL-1β), IL-6, IL-10, tumor necrosis factor (TNF)-α, interferon-gamma (IFN)-γ, etc., is thought to be one of the main contributing factors to cytokine storm in COVID-19 patients [2, 10], even though the specific mechanism is still unclear. It was suggested that pro-inflammatory cytokines produced by immune system might also interact with the cytokine network of the central nervous system (CNS), particularly in situations where the blood-brain barrier (BBB) is damaged [2]. The overlapping immune and CNS cytokine networks may lead to neuroinflammation accompanied by immune cell infiltration, microglia activation, and reactive gliosis [11]. As a result, increased oxidative stress and neurotoxicity can cause damage to neural tissue leading to formation of demyelination areas in white and gray matter of CNS [11, 22]. Taking into consideration these pathways and the possible devastating effect of cytokine storm on «high-risk» patients, such as suffering from autoimmune diseases, COVID-19 may be a contributory factor for the triggering or worsening of multiple sclerosis (MS) clinical manifestation [11, 13].

Multiple sclerosis (MS) is a chronic, immune-mediated disease of the CNS. Multiple focal demyelinating plaques (also known as lesions) in both white and gray matter of the brain and spinal cord, along with inflammation, gliosis, and neuro-axonal damage, are the main pathological hallmarks of MS [4, 12], which result in irreversible and progressive physical and cognitive disability [5]. Despite what we know so far about MS pathophysiology, there is no effective therapy for this disease, and its prevalence rate has been rising steadily, year by year, resulting in the significant health and economic costs.

Growing evidences reinforce the view that hemostasis system, on the one hand, is a critical target for SARS-CoV-2 infection [8, 28] and, on the other hand, some hemostasis factors can be involved in the pathological mechanisms leading to the nerve fiber damage and triggering the deterioration of MS symptoms [31]. Thus, pathophysiology of MS is characterized by increased BBB permeability, which allows some hemostasis factors to infiltrate into the brain parenchyma and maintain inflammatory responses and microglia activation [32, 33]. In this study, we hypothesize that hemostatic factors that have been dysregulated in COVID-19, may serve as risk factors for the neurodegenerative events in MS patients. However, there is limited research regarding influence of SARS-CoV-2 infection on hemostasis system functioning in individuals suffering from MS.

THE AIM

The current work aimed to investigate plasma levels of main coagulation and fibrinolytic factors in MS patients with and without COVID-19 history.

MATERIALS AND METHODS

This study was conducted in accordance with the ethical standards the 1964 Declaration of Helsinki, and approved by the ethics committee of Taras Shevchenko National University of Kyiv (Kyiv, Ukraine). Subjects seen at University Clinic of the Bogomolets National Medical University (Kyiv, Ukraine) from January 2021 to August 2022 included 97 MS patients (34M/63F, median age: 43 years) of which: 41 were COVID-19 convalescent patients who were positive in the past 3-6-month period, but currently negative, as determined by testing nasopharyngeal swabs (MS+COVID group) and 56 did not suffer from COVID-19 previously (MS group). The control group included 30 subjects, all of whom were SARS-CoV-2 negative by nasopharyngeal swab at the time of the blood draw. We excluded all those individuals who had cardiovascular and cerebrovascular diseases; were on hemostatic medications; had any acute or chronic disorders that can affect the hemostasis system. Written informed consent was obtained from all participants.

Plasma was obtained from freshly drawn blood stabilized with sodium citrate. Blood samples were centrifuged for 15 min at 2500 g, and plasma was aliquoted and stored at -80°C until use. Prior to analysis, frozen plasma samples were placed into a 37 °C water bath, thawed for five to ten minutes, and mixed by gentle inversion.

Fibrinogen concentration was determined spectrophotometrically by the technique previously described [25]. Briefly, fibrin clot formed after the addition of thrombin (2 NIH) was dissolved using 0.15 % acetic acid. The optical density (OD) of samples was measured at wavelengths of 280 and 320 nm. The fibrinogen concentration (g/L) was calculated using the formula: (OD280 – OD320) × 255 / 1.506; where 255 represents the conversion factor of the fibrinogen concentration in the sample volume to its plasma concentration, and 1.506 represents the fibrin extinction coefficient at 280 nm.

The concentration of soluble fibrin monomeric complexes (SFMC) was measured by means of o-phenanthroline technique [18]. This method is based on the assessment of time needed to form fibrin particles after addition of 0.78 % o-phenanthroline solution.

Determination of plasma levels of hemostasis factors, such as prothrombin, plasminogen, tissue-type plasminogen activator (tPA), plasminogen activator inhibitor-1 (PAI-1), protein C (PC), soluble thrombomodulin (TM) was performed by means of enzyme-linked immunosorbent assay (ELISA) [19, 21]. Briefly, plasma samples were diluted 1:100 with 0.05 M Tris-HCl buffer (pH 7.4) and added into the wells of ELISA plates. After incubation for 1 hour at 37 °C, the plates were washed with washing buffer (0.05 M Tris-HCl buffer, pH 7.4, containing 0.05 % Tween-20), and blocked with 3 % nonfat dry milk for overnight. After washing, the plates were coated with monoclonal antibodies

(Santa Cruz Biotechnology, Inc, USA) against the targeted antigens, and incubated for 1 hour at 37 °C. Then, plates were incubated for 1 hour at 37 °C with the corresponding horseradish peroxidase-conjugated secondary antibodies (Sigma-Aldrich, USA). The reaction was visualized using substrate solution containing o-phenylenediamine and hydrogen peroxide. The reaction was stopped by 2.5 M H2SO4, and optical density was measured using a microplate spectrophotometer (BioTek Instruments, Inc., USA) at a wavelength of 492 nm.

Potential plasminogen activity was determined by method described previously [20, 26]. Briefly, plasma was diluted 1:50 with 0.05 M Tris-HCl buffer, pH 7.4. The reaction mixture (final volume was 250 μL) consisted of 0.05 M Tris-HCl buffer, pH 7.4, diluted plasma sample, and streptokinase, a plasminogen activator from *Streptococcus uberis* (final concentration was 50 IU). Mixture was incubated for 5 min at 37°C, then chromogenic substrate S2251 (RENAU, Ukraine) was added (final concentration was 3 mM). The optical density of the samples was measured using a microplate spectrophotometer (BioTek Instruments, Inc., USA) at a wavelength of 405 nm. The amount of free p-nitroaniline produced was directly proportional to plasminogen activity.

Measurement of inhibitory potential of α-2-antiplasmin was performed by method described previously [20, 26]. Briefly, plasma was diluted 1:3 with 0.05 M Tris-HCl buffer, pH 7.4. The reaction mixture (final volume was 250 μL) consisted of 0.05 M Tris-HCl buffer, pH 7.4, diluted plasma sample, and plasminogen. Mixture was incubated for 5 min at 37°C, then chromogenic substrate S2251 (RENAU, Ukraine) was added (final concentration was 3 mM). The optical density of the samples was measured using a microplate spectrophotometer (BioTek Instruments, Inc., USA) at a wavelength of 405 nm. The amount of free p-nitroaniline produced was inversely proportional to the potential inhibitory activity of α-2-antiplasmin.

The qualitative detection of immunoglobulin M (IgM) and immunoglobulin G (IgG) antibodies to SARS-CoV-2 in blood plasma was done by chemiluminescence immunoassay ussing the reagent kit «MAGLUMI 2019-nCoV IgM/IgG» (Shenzhen New Industries Biomedical Engineering Co., Ltd., China). The results are expressed in absorbance unit AU/mL. Acceding to the operating instructions, a result less than 1.00 AU/mL (<1.00 AU/mL) was considered to be non-reactive, while a result greater than or equal to 1.00 AU/mL (≥1.00 AU/mL) was considered to be reactive.

All statistical tests were performed using STATISTICA Package, version 12.0 (StatSoft. Inc., USA). For studied variables, we reported means with SE and medians with IQRs. For categorical variables (gender), we reported absolute numbers and percentages. We used the Shapiro-Wilk test to clarify the distribution of the data and the Mann–Whitney U test or the Kruskal-Wallis test to compare the medians of different variables. A $p<0.05$ was considered statistically significant.

RESULTS

The group of MS patients included 63 women and 34 men, ranging in age from 35 to 45 years. In this study, we included only those patients with a disease duration for 4.5±1.5 years. At the time of blood collection, all healthy donors and patients with MS were additionally tested for the presence of anti-SARS-CoV-2 antibodies (both IgM and IgG) in order to verify infection in the case of latent disease. The basic characteristics of the groups are summarized in table 1. As can be seen, either healthy volunteers or MS patients had negative IgM serology that indicates that all participants had no acute/recent COVID-19 infection. On the other hand, based on the IgG serology MS patients were divided in two groups: (1) MS group (n=56) – MS patients, who did not suffer from COVID-19 previously; (2) MS+COVID group (n=41) – MS patients who were positive on COVID-19 in the past 3-6-month period, but currently negative. The exact time of COVID-19 diagnosis was additionally confirmed on the basis of previous results of RT-PCR on nasopharyngeal swabs.

Table 1

Basic characteristics of the MS patients and healthy controls (HC)

Parameter	Groups		
	HC (n = 30)	MS (n = 56)	MS+Covid (n = 41)
Age (years)	41 ± 4	40 ± 5	40 ±5
Gender:			
male, n (%)	10 (33)	20 (36)	14 (41)
female, n (%)	20 (67)	36 (64)	27 (59)
Disease duration (years)	-	4.4 ± 1.5	4.6 ± 1.3
anti-SARS-CoV-2 IgM (AU/mL)	<1.0	<1.0	<1.0
anti-SARS-CoV-2 IgG, (AU/mL)	0.18(0.27)	0.12(0.23)	4.70(4.40)*

Age and disease duration in years are reported as Mean ± SEM. For the anti-SARS-CoV-2 IgG, the median (interquartile range) is given. * $p < 0.0001$ vs. both HC group and MS group

Plasma prothrombin and fibrinogen levels were elevated in MS patients with and without COVID-19, compared to healthy controls (fig. 1; A, and B, respectively). On the other hand, prothrombin level in plasma of MS patients after suffering from SARS-CoV-2 infection was not significantly different from that in MS patients, who did not have the coronavirus infection in anamnesis ($p = 0.98$), while plasma fibrinogen level was slightly decreased ($p = 0.038$) in MS+COVID group compared to MS group (fig. 1 B).

Comparison between both MS groups, and healthy controls (HC) revealed significant differences in D-dimer levels (MS, $p = 0.0003$; MS+COVID, $p = 0.008$), but no difference within patients' subgroups (MS, and MS+COVID, $p = 0.36$) was detected for this parameter (fig. 1 C). As seen (fig. 1 D), plasma SFMC concentrations were significantly greater in MS patients both with or without COVID-19 history (MS, $p < 0.0001$; MS+COVID, $p < 0.0001$), but this parameter did not differ between two MS groups ($p = 0.11$).

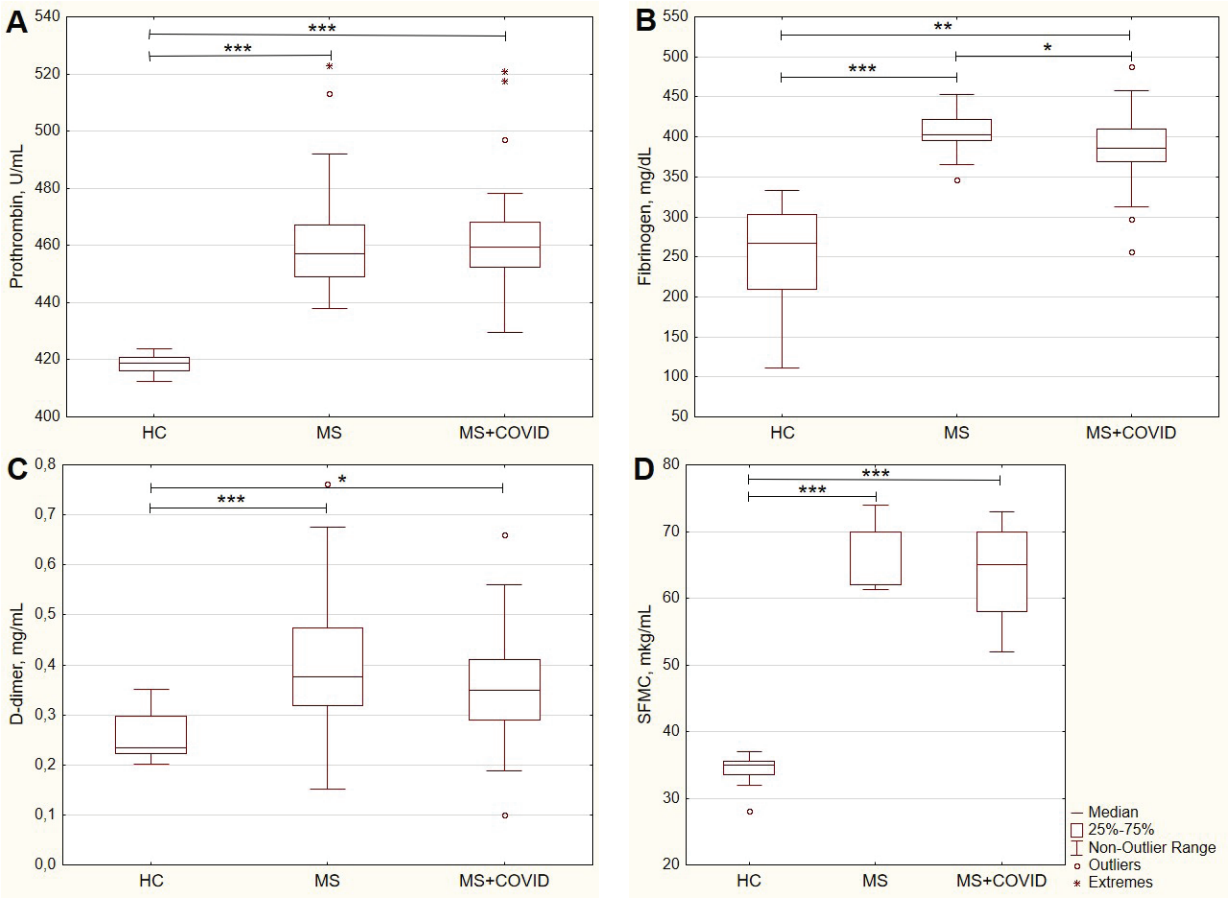

Figure 1. Concentrations of prothrombin (A), fibrinogen (B), D-dimer (C), and SFMC (D) in plasma of MS patients and healthy controls (HC); *p < 0.05; **p < 0.005; ***p < 0.0005

Protein C (PC), and plasma soluble thrombomodulin (TM) levels were also investigated (fig. 2; A, and B, respectively). Significant differences were detected for both studied parameters. In particular, pairwise analysis revealed differences between PC levels within groups (fig. 2A): HC and MS+COVID ($p < 0.0001$), as well as MS and MS+COVID ($p < 0.0001$). Difference was not detected between MS group and HC ($p = 0.58$). In the case of the plasma soluble TM concentration (fig. 2B), this parameter was higher in MS group as compared to the HC group ($p = 0.008$), while MS+COVID patients showed more significant differences in TM value as compared to the HC group ($p < 0.0001$). A significant difference was also observed in TM levels ($p = 0.03$) for MS patients with and without COVID-19 history (fig. 2B).

Figure 3 shows the plasminogen level, and its activity (A, and B, respectively) in plasma of MS patients and healthy controls. The data showed that in both groups of MS patients, plasma plasminogen levels were significantly decreased compared to HC group ($p < 0.0001$); on the other hand, this parameter did not differ significantly between MS and MS+COVID groups ($p = 0.59$). As seen (fig. 3B), patients of the MS group had a decreased level of potential plasminogen activity compared to HC group ($p = 0.0008$). At the same time, the plasma level of the potential plasmin activity in MS patients, who had recovered from COVID-19, was not markedly different from that value in healthy controls (fig. 3B).

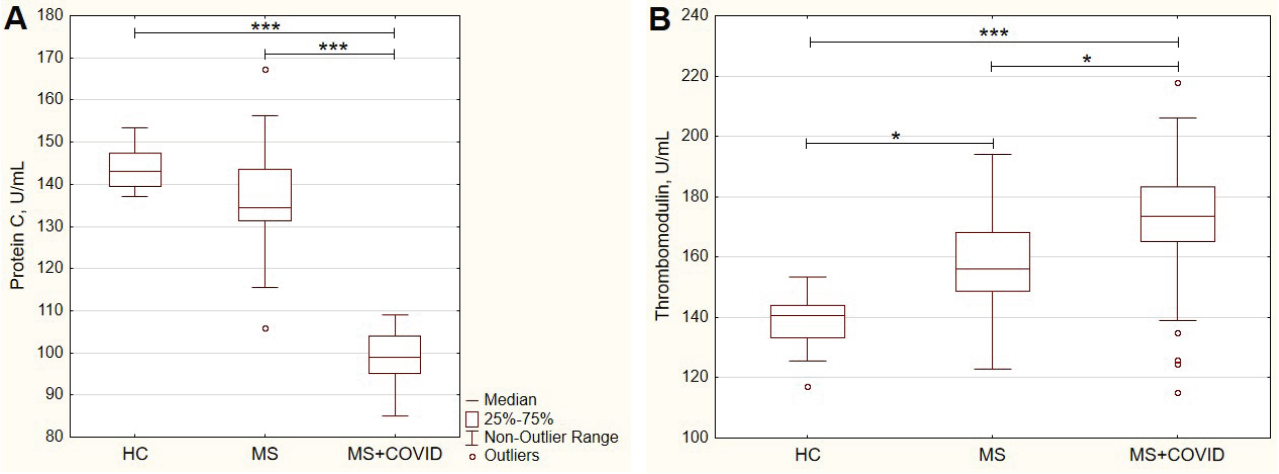

Figure 2. Protein C (A), and soluble thrombomodulin levels in plasma of MS patients and healthy controls (HC); *p < 0.05; **p < 0.005; ***p < 0.0005

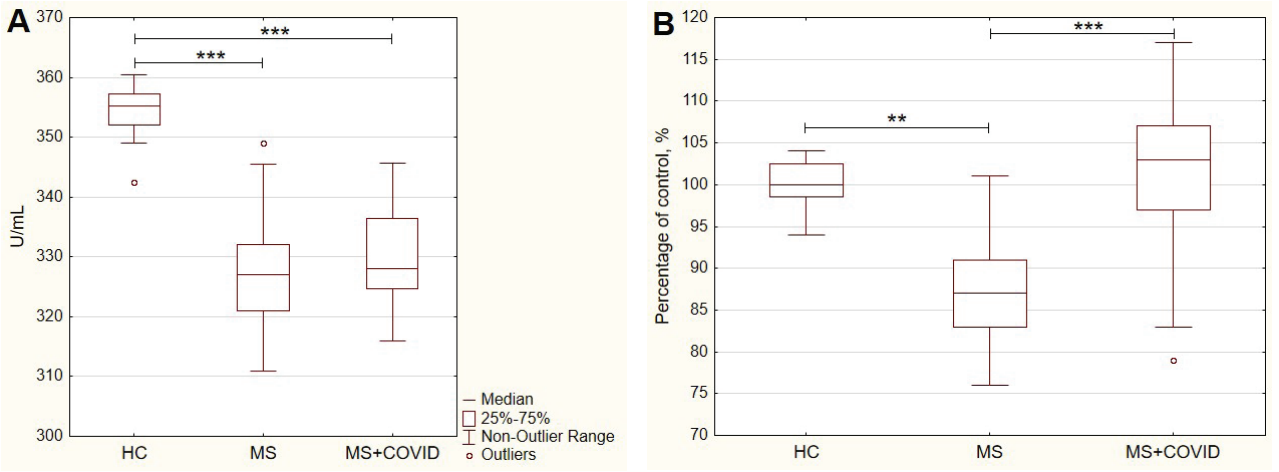

Figure 3. Plasminogen level (A), and its potential activity (B) in plasma of MS patients and healthy controls (HC); *p < 0.05; **p < 0.005; ***p < 0.0005

Plasma tPA, and PAI-I levels were also investigated (fig. 4; A, and B, respectively). The levels of plasma tPA were significantly reduced in patients of MS group ($p = 0.0003$) and MS+COVID group ($p<0.0001$), compared to healthy controls (fig. 4A). At the same time, differences were not detected between both MS groups ($p = 1.00$). Compared with the healthy controls, patients with MS, independent on the coronavirus infection in anamnesis, had increased levels of plasma PAI-I ($p<0.0001$). However, this parameter did not differ between two MS groups ($p = 0.53$).

Significant differences were also observed in the levels of α-2-antiplasmin activity for MS patients and healthy controls (fig. 4C). Compared with the value of HC group, patients of MS group had an increased level of plasma α-2-antiplasmin activity ($p = 0.012$). To note, MS patients after suffering from SARS-CoV-2 infection had more significant differences in plasma α-2-antiplasmin activity compared to ether HC group or MS group ($p<0.0001$, and $p<0.0001$, respectively).

DISCUSSION

Recently, there is increased attention to the coagulation factors as potential triggers the neurodegenerative processes in MS [31]. It has been shown that in MS patients blood-brain barrier becomes more permeable, and some coagulation factors, for example fibrinogen, may infiltrate into the brain parenchyma, and deposit in the brain tissues, playing an important role in the activation of CNS inflammation, inhibition of tissue repair, and induction of lesion formation [7, 30, 31]. Such findings provide strong evidence that fibrinogen can be a component of the pathological cascade that causes neuronal dysfunction in MS. However, the role of other coagulation factors in the progression of neuronal lesions is not fully understood. On the other hand, hemostasis system is a critical target for SARS-CoV-2 infection [8, 28]. Therefore, a careful study of the hemostasis system component elements in MS patients depending on the presence of coronavirus infection in anamnesis may help to understand some of the pathological mechanisms that might be involved in the disease progression occurs after COVID-19.

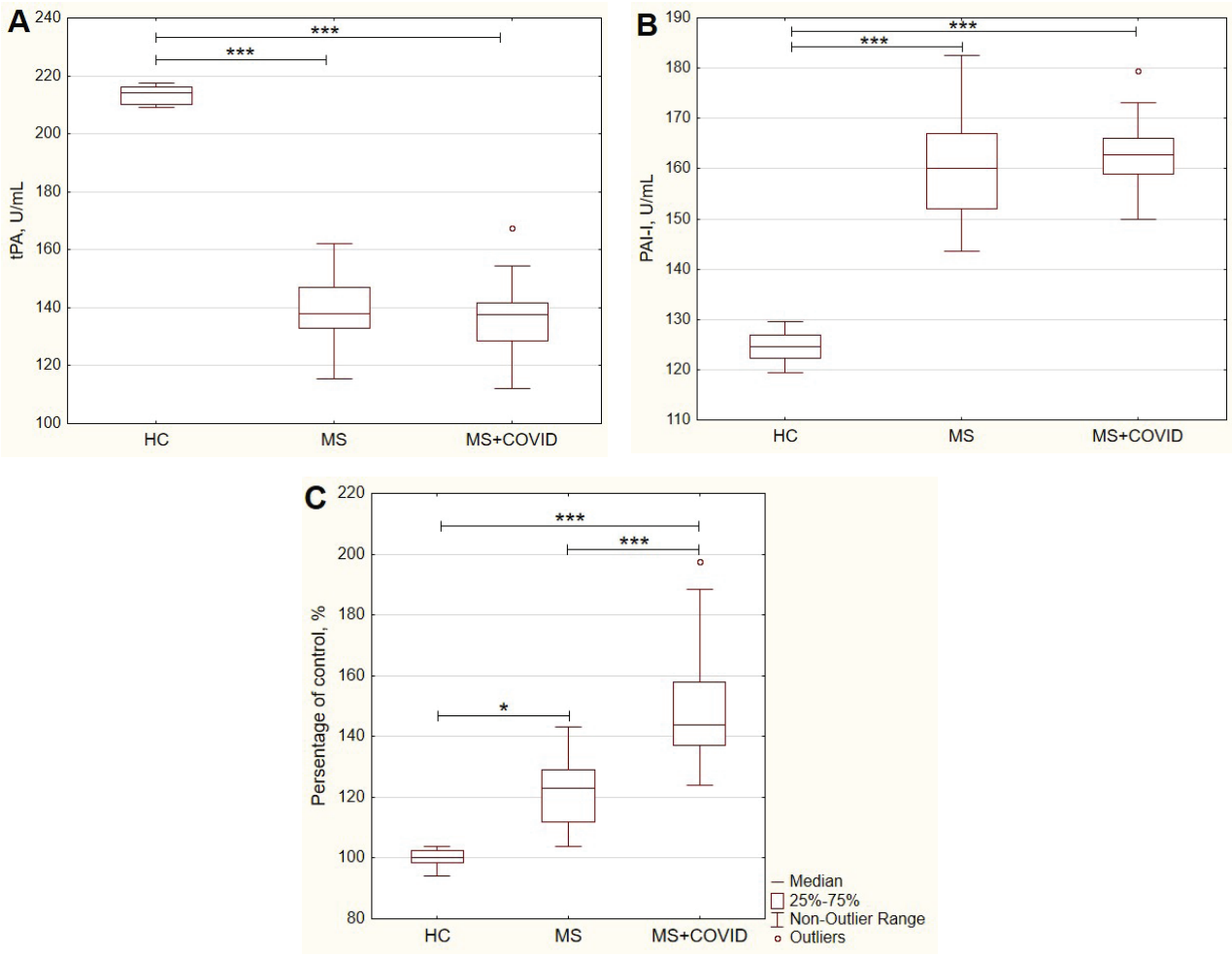

Figure 4. Levels of tPA (A) as well as PAI-I (B), and α-2-antiplasmin activity (C) in plasma of MS patients and healthy controls (HC); *p < 0.05; **p < 0.005; ***p < 0.0005

According to the obtained results, the two main coagulation factors, namely prothrombin and fibrinogen, were increased in plasma of MS patients (fig. 1A, and B). As seen, coronavirus infection did not affect the prothrombin level in MS, but a slight decrease in the level of fibrinogen was noted in MS patients who suffered from a SARS-CoV-2 infection previously. Such changes can be explained by the effect of viral infection on the BBB permeability, which, in turn, can lead to increased infiltration of fibrinogen from serum to brain tissues [17].

The cleavage of fibrinogen molecules into fibrin monomers which interact lately to form insoluble fibers, occur under the action of thrombin when the coagulation pathway is activated [23]. In the very early stages of blood coagulation, fibrin monomers will form the soluble fibrin monomer complexes (SFMC). Thus, the appearance of detectable SFMC in the plasma of MS patients (fig. 1D) indicates that thrombin has been generated and coagulation has been activated. The fibrinolytic process, mostly mediated by plasmin activity, will break down the fibrin clot that was formed by coagulation activation to produce fibrin degradation products, such as D-dimers [23]. Thus, the appearance of D-dimers in the plasma of MS patients (fig. 1C) may confirm the presence of fibrin degradation products as well as shows that both the coagulation cascade (via thrombin formation) and fibrinolytic cascade (via plasmin generation) were activated. It is important to note, we did not notice significant differences in both D-dimers and SFMCs in MS patients who previously suffered from a SARS-CoV-2 infection, compared to MS patients who did not have COVID-19 in anamnesis (fig. 1C, and D).

The level of plasma protein C, which play a key role as anticoagulant by inactivation of coagulation factors Va and VIIIa [6], was significantly lower in the MS+COVID group than those in the groups of healthy volunteers and MS patients who did not suffer from coronavirus infection previously (fig. 2A). Our results support evidence from previous study [9], and may indicate that SARS-CoV-2 infection is accompanied by a state of hypercoagulability, and is a risk factor for venous thromboembolism development.

Thrombomodulin (TM) is the endothelial cell transmembrane receptor for thrombin [29], which inhibits the

thrombin ability to catalyze clot formation, and switches the thrombin function into a protein-C activator. On the other hand, soluble TM may appear in the circulation as cleavage product of membrane form produced during acute and chronic inflammatory responses [3, 24]. Elevated levels of soluble TM in MS patients may be a result of inflammation process. We also noted a significant difference in TM levels after SARS-CoV-2 infection (fig. 2B) that could be explained by increased level of endothelial cell damage as well as intensification of inflammation; such changes could be a predictor of poor post-COVID-19 cardiovascular outcomes in MS patients.

Plasminogen is a zymogen form of plasmin, which mediates the fibrin cleavage into soluble degradation products, particularly the D-dimers. The most abundant plasminogen activator is tissue-type plasminogen activator (tPA). Except the function in the fibrinolytic system, tPA is also involved in the neuronal cell signaling, microglial activation and/or inflammation, regulation of cerebrovascular integrity [16, 31]. The activity of tPA is regulated by specific plasminogen activator inhibitors (PAIs) among which the most abounded is PAI type 1 (PAI-1) [16]. Decreased levels of both plasminogen antigen and plasminogen activity were observed in MS patients (fig. 3). The lower plasminogen level and tPA level in the MS patients are in line with the earlier findings [1, 16], however, there is no exact explanation for such changes. We can make several suggestions: firstly, plasminogen from plasma might diffuse across a damaged BBB into brain parenchyma; secondly, plasma plasminogen could be converted to its active form, plasmin, and involved into the formation plasmin-α2-antiplasmin complexes. The second hypothesis is consistent with the results of increased α2-antiplasmin activity in MS patients (fig. 4C).

CONCLUSIONS

In conclusion, significant progress has been made in understanding of the effects of a SARS-CoV-2 infection on the coagulation/anticoagulation systems under MS. The damaged BBB is considered to be a key event in the MS pathophysiology, and may lead to the penetration of blood hemostasis factors into the CNS. Besides their role in hemostasis, coagulation factors can trigger the complex cascade of inflammatory response, causing immune activation and neurodegenerative events in MS. Our findings revealed the changes in hemostasis in MS patients, however, the exact functions of the components of both coagulation and fibrinolytic pathways in the pathophysiology of MS still remain to be elucidated. Furthermore, the results of current study showed that a SARS-CoV-2 infection has a limited effect on hemostasis in MS patients, causing statistically significant changes in only a few parameters, namely levels of protein C and thrombomodulin levels, and α-2-antiplasmin activity. Early studies have shown the contribution of COVID-19 in altered hemostasis. New molecular details regarding the impotence of such hemostasis components for MS pathophysiology, particularly their involvement in immune responses and lesion progression, could favor new understanding new understanding of the MS pathology after coronavirus infection.

The prospects for further research. The findings of the present research would be beneficial to complete with an analysis of correlation relationships between the levels of selected hemostatic factors and the severity of MS. Determination of hemostasis components in cerebrospinal fluid would also be interesting and could lead to improvements in the predictability of neurodegenerative outcomes. To draw a final conclusion on the association between SARS-CoV-2 infection and either hemostatic abnormalities or poor prognosis in MS subjects, more patients should be recruited for the study. Larger sample sizes allow us to control the risk of reporting false findings, providing greater statistical power, and producing more precise estimates.

FUNDING AND CONFLICT OF INTEREST

There was no conflict of interest in the course of the work. No special funding was provided for the study.

COMPLIANCE WITH ETHICAL REQUIREMENTS

The present study was conducted in accordance with the basic principles of the European Convention of Human Rights and Biomedicine, World Medical Association Declaration of Helsinki on the ethical principles for medical research involving human subjects, and current Ukrainian regulations. The study protocol was approved by the ethics committee of Taras Shevchenko National University of Kyiv (Kyiv, Ukraine). The written informed consent was obtained from all participants.

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Резюме

ПОКАЗНИКИ СИСТЕМ КОАГУЛЯЦІЇ ТА ФІБРИНОЛІЗУ У ПАЦІЄНТІВ З РОЗСІЯНИМ СКЛЕРОЗОМ З ТА БЕЗ COVID-19 В АНАМНЕЗІ

Тетяна І. Галенова[1], Наталія Г. Ракша[1], Тетяна Б. Вовк[1], Віталій Л. Карбовський[2], Світлана М. Шоломон[3], Володимир С. Мельник[3], Олексій М. Савчук

1 – Київський національний університет імені Тараса Шевченка, м. Київ, Україна
2 – Товариство з обмеженою відповідальністю «Біофарма Плазма», директор з науки та технології, м. Біла Церква, Україна
3 – Національний медичний університет імені О. О. Богомольця, м. Київ, Україна

Мета дослідження. Дослідити рівні основних коагуляційних і фібринолітичних факторів у плазмі крові хворих на РС з та без COVID-19 в анамнезі.
Матеріали та методи. У це дослідження було залучено 127 осіб, у тому числі 97 хворих на РС та 30 здорових донорів, що склали контрольну групу. Пацієнти з РС були розділені на дві підгрупи: група РС+Covid (n=41) – пацієнти з РС, у яких був лабораторно підтверджений діагноз COVID-19 за останні 3-6 місяців та група РС (n=56) – пацієнти з РС, які раніше не хворіли на COVID-19. Визначення в плазмі крові протромбіну, плазміногену, тканинного активатора плазміногену (tPA), інгібітору активатора плазміногену-1 (PAI-1), протеїну С (ПС), розчинного тромбомодуліну (ТМ) проводили методом імуноферментного аналізу. Спектрофотометричні методи були використані для визначення концентрації фібриногену, розчинних фібринмономерних комплексів (РФМК), а також потенційної активності плазміну та інгібуючого потенціалу α-2-антиплазміну.
Результати. Група РС характеризувалася підвищеними рівнями протромбіну, фібриногену, D-димеру, РФМК, плазмового ТМ, порівняно з групою здорових донорів (ЗД), тоді як концентрація ПС не відрізнялася між групами РС та ЗД. Рівень плазміногену, а також рівень потенційної активності плазміну в плазмі були значно знижені у пацієнтів з РС, порівняно з групою ЗД. Рівень tPA у плазмі був також знижений, тоді як рівень PAI-I, навпаки, підвищений у пацієнтів з РС, порівняно з ЗД. У пацієнтів групи РС спостерігався підвищений рівень активності α-2-антиплазміну, порівняно з групою ЗД. Слід зазначити, що більшість досліджуваних параметрів не відрізнялися між двома підгрупами РС, за винятком протеїну С, рівня розчинного ТМ та активності α-2-антиплазміну в плазмі.
Висновки. Результати нашого дослідження показали, що у хворих на РС змінені показники гемостазу; однак необхідні подальші дослідження, щоб з'ясувати зв'язок між окремими компонентами коагуляційної та фібринолітичної систем і патофізіологією РС. Крім того, наші результати продемонстрували, що інфекція SARS-CoV-2 мала обмежений вплив на параметри гемостазу у пацієнтів з РС, викликаючи зміни лише кількох параметрів, серед них рівні ТМ, протеїну С, а також активність α-2-антиплазміну.

Ключові слова: **розсіяний склероз, інфекція SARS-CoV-2, фактори гемостазу, коагуляція, фібриноліз**