

Is Thrombophilic Genetic Profile Responsible for an Acute Ischemic Stroke in a COVID-19 Male Patient?

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Alexandru Burlacu^{1,2} , Bogdan Artene¹, Radu Crisan-Dabija^{2,3},
Iolanda Valentina Popa^{2,4} , and Adrian Covic^{2,5}

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Mezalek et al. presented a recent study (published in August 2020 in the *Clinical and Applied Thrombosis/Hemostasis*), a comprehensive review of the COVID-19 induced coagulopathy with its particular traits, the specificity of thromboembolic events and potential therapeutic interventions.¹ This paper pertinently emphasizes the importance of a coagulopathy in the clinical course of COVID-19. Thrombotic events influence the clinical deterioration process, thus linking the hypercoagulable state with disease severity.

Several possible thrombotic sites are distinctively described “from classic deep vein thrombosis and pulmonary embolism to unusual thrombosis of central lines or arterial catheters, very early thromboses of extra-renal hemodialysis filters, and ECMO cannulas” providing valuable information for clinical practice. Additionally, the paper mainly describes the mechanisms of the COVID-19 coagulopathy at the intersection of inflammation and coagulation, highlighting distinctive elements that differentiate it from the classical diffuse intravascular coagulation.

In this particular context, the authors underline that the conventional clinical assessment of the risk of thrombotic events may not be efficient due to disease’s particular evolution. Nevertheless, there is a legitimate need for a rigorous thrombotic risk assessment to implement suitable anticoagulation strategies.

As a contribution to our colleagues’ work, we envision a new, well-sustained hypothesis that could bring more clarity into the process of assessing the COVID-19 patients’ risk for thrombosis. We consider that the mechanisms of COVID-19 coagulopathy are not limited to the dynamics of D-dimers and fibrinogen nor the impact of the well-described “cytokine storm” and its inflammatory consequences on the activation of endothelial cells and tissue factor expression. A genetic component related to a pre-existing prothrombotic status might also be involved, explaining the heterogeneous variety of disease forms.

Our assumption is based on several considerations.

Firstly, the process of “viral sepsis” has been described in COVID-19, showing a substantial similarity with the classical condition of sepsis. Here, a validated theory states that several thrombophilic mutations affect patients’ clinical response.² Secondly, racial and ethnic genetic differences are responsible for significant dissimilar thrombotic risks among various nations.³ Thirdly, apolipoprotein E (ApoE) polymorphism and its prothrombotic genotypes were associated with increased mortality in confirmed COVID-19.⁴ Fourthly, the angiotensin-converting enzyme (ACE) D/I polymorphism is a risk factor for thrombosis and mortality in ARDS.⁵ Finally, the prothrombotic genotypes of ACE D/I and angiotensinogen (AGT M235 T) could explain the observed link between thrombosis and disease severity, due to the strong interactions of SARS-CoV-2 with the renin-angiotensin-aldosterone system.⁶

We recall a particular case of a 47-year-old male, from our center, with an acute ischemic stroke. Three days before the neurological event, the patient presented with mild respiratory symptoms erroneously interpreted as a non-COVID-19 pulmonary infection. Our patient was referred to the neurology service 3 hours after a sudden onset of weakness of his left arm

¹ Department of Interventional Cardiology, Cardiovascular Diseases Institute, Iasi, Romania

² “Grigore T. Popa” University of Medicine and Pharmacy, Iasi, Romania

³ Pulmonology Department, Clinic of Pulmonary Diseases, Iasi, Romania

⁴ Institute of Gastroenterology and Hepatology, Iasi, Romania

⁵ Nephrology Clinic, Dialysis and Renal Transplant Center—“C.I. Parhon” Hospital, Iasi, Romania

Corresponding Author:

Iolanda Valentina Popa, Institute of Gastroenterology and Hepatology, Bd Independenței No 1, Iași, 700111, Romania.

Email: iolivp@gmail.com



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Table I. Thrombophilic Profile of the 37-Year-Old Patient Diagnosed With COVID-19 and Stroke.

Prothrombotic genotypes	Patient's profile
Factor V Leiden	Negative
Factor V 4070 A>G (Hr2)	Negative
Factor II G20210A	Negative
MTHFR C677T	Negative
MTHFR A1298C	Positive (heterozygous genotype)
CBS 844ins68	Negative
PAI-1 4G/5G	Negative
Glycoprotein IIIa T1565C (HPA-1a/b)	Negative
ACE D/I	Positive (heterozygous genotype)
ApoE	Positive (e3/e4)
AGT M235T	Positive (M/T heterozygous genotype)
Angiotensin II type I receptor (ATR-1) A1166C	Negative
Fibrinogen—455 G>A	Negative
Factor XIII Val34Leu	Positive (V/L heterozygous genotype)

and leg associated with left facial droop and vertigo. On clinical examination, he was confused, with left upper and lower limb hemiplegia, and dysarthria. He resulted positive for the SARS-CoV-2 RT-PCR test at admission. He had no prior medical history.

Emergent non-enhanced computed tomography revealed no cerebral hemorrhage. Three and a half hours after the onset of symptoms, intravenous tissue plasminogen activator (IV tPA—alteplase) was administered according to the European guidelines. After thrombolysis, patient's neurologic status progressively improved. A CT scan obtained 6 hours later was negative for cerebral hemorrhage or acute ischemic lesions. Our patient received a continuous infusion of unfractionated heparin (UFH) (1,200 U/h) for 24 hours after the procedure. Carotid and vertebral arteries demonstrated no significant lesions on subsequent assessments. Our patient was discharged a week later with routine neurological and pulmonary clinical examination.

At 1-month follow-up, he manifested neurologically normal status without residual deficits. After discharge, transesophageal echocardiography was performed. Due to the assumption of a patent foramen ovale, a bubble study was conducted with a negative result.

Considering that other risk factors for thrombosis were excluded, thrombophilia screening panel was recommended, including factor V Leiden, factor V 4070 A>G (Hr2), factor II G20210A, methylenetetrahydrofolate reductase (MTHFR) C677 T, MTHFR A1298C, cystathionine β -synthase (CBS) 844ins68, plasminogen activator inhibitor (PAI)-1 4G/5G, glycoprotein IIIa T1565C (HPA-1a/b), ACE D/I, apolipoprotein E

(ApoE), AGT M235 T, angiotensin II type 1 receptor (ATR-1) A1166C, fibrinogen—455 G>A and factor XIII Val34Leu.


The tests resulted positive for ApoE e3/e4, MTHFR A1298C heterozygous, ACE D/I heterozygous, AGT M235 T heterozygous, and FXIII Val34Leu heterozygous (Table 1).

To further progress with our assumption, we registered a thorough clinical trial (<https://www.clinicaltrials.gov/ct2/show/NCT04519398>) that aims to validate our hypothesis on the involvement of thrombophilic genetic profiles in the novel coronavirus disease. Besides the main outcome of our study concerning the number of patients with thrombophilic profile and RAAS components alterations, several secondary outcomes will also be of interest to explore in the future in order to integrate a meaningful and global picture of hereditary coagulation profiles in COVID-19 patients. For instance, detecting particular alterations of the bleeding risk, mortality, ARDS incidence, and intensive care unit admissions in the presence of a thrombophilic profile context may be powerful traits to investigate in an extended protocol. We strongly suspect that subtle genetic risk factors for thrombotic events may influence the COVID-19 course, might hold the key to understanding the significant heterogeneity of COVID-19 manifestations, and may prove useful in assessing the COVID-19 patients' risk for thrombosis and severe disease.

Authors' Note

Alexandru Burlacu and Bogdan Artene contributed equally.

ORCID iD

Alexandru Burlacu  <https://orcid.org/0000-0002-3424-1588>

Iolanda Valentina Popa  <https://orcid.org/0000-0002-0597-8839>

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