



Angiogenesis, hereditary hemorrhagic telangiectasia and COVID-19

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Received: 28 September 2020 / Accepted: 5 October 2020 / Published online: 14 October 2020
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Abstract

Hereditary hemorrhagic telangiectasia (HHT) is a rare autosomal-dominant disease characterized by pathologic angiogenesis that provokes vascular overgrowth. The evidence about the influence of Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) in patients with rare diseases is scarce. We aimed to know the prevalence of coronavirus disease 2019 (COVID-19) in HHT patients. The HHT pathogenic angiogenesis and endothelial injury in COVID-19 are discussed using data from RiHHTa (Computerized Registry of Hereditary Hemorrhagic Telangiectasia) registry. RiHHTa is an open, multicenter, prospective, observational registry including adult patients with HHT. A 27-item survey that captured clinical data of admitted HHT patients for COVID-19 was distributed to all RiHHTa investigators from June 8th to June 24th 2020. Only one out of 1177 HHT patients was admitted for COVID-19 pneumonia. She is a 74 years-old woman with a pathogenic variant in *ACVRL1* gene. Her clinical course did not involve mechanical ventilation or worsening epistaxis, and she was successfully discharged after two weeks. The endothelial damage and the consequent angiogenic process in COVID-19 patients deserve further investigation.

Keywords Hereditary hemorrhagic telangiectasia · Rare diseases · Angiogenesis · Coronavirus disease 2019 (COVID-19) · Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2)

Abbreviations

HHT	Hereditary hemorrhagic telangiectasia
ENG	Endoglin
ACVRL1	Activin A receptor type II-like 1
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus-2
COVID-19	Coronavirus disease 2019

RiHHTa	Computerized Registry of Hereditary Hemorrhagic Telangiectasia
VEGF	Vascular endothelial growth factor
ICU	Intensive care unit

Dear Editor:

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Hereditary hemorrhagic telangiectasia (HHT) is a rare autosomal-dominant disease characterized by vascular malformations. Disease-causing variants are mostly detected in endoglin (*ENG*; encoding endoglin) and activin A receptor type II-like 1 (*ACVRL1*; encoding activin receptor-like kinase-1) genes. Both encoded proteins highly impact in angiogenesis as their loss-of-function provokes vascular overgrowth, mainly due to over-activation of phosphatidylinositol 3-kinase signalling [1].

The Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) cause the coronavirus disease 2019 (COVID-19), that has spread worldwide [2, 3]. Since the COVID-19 outbreak in Wuhan (China), many articles addressing COVID-19 have been published. However, little is known about the influence of SARS-CoV-2 in patients with rare diseases, so there is a need for further clinical,

translational and multicentric studies. Though knowledge of the pathogenic mechanisms of COVID-19 is still evolving, endothelial dysfunction can be considered a linchpin [4]. As previous data were lacking, we aimed to know the prevalence of COVID-19 pneumonia in HHT patients.

RiHHTa (Computerized Registry of Hereditary Hemorrhagic Telangiectasia) is an open, multicenter, prospective, observational registry including adult patients with HHT and developed within the Rare Diseases Working Group of the Spanish Society of Internal Medicine [1]. RiHHTa has an online design (accessible from <https://rihhta.healthincode.com>) available in Spanish or English with individual encoded access for each researcher and counted on the nonremunerated collaboration of the genetic studies company Health in Code (A Coruña, Spain). The design of the RiHHTa registry was approved by the Ethics Committee of the Hospital Universitari de Bellvitge. The rationale and methodology of RiHHTa have been published elsewhere [1]. For this study, we focused in those HHT patients who required admission for COVID-19 pneumonia, so we created a 27-item survey that captured clinical data of hospitalized patients with both diseases. From June 8th to June 24th 2020, an electronic survey was distributed to all RiHHTa investigators. The survey was responded by investigators from 22 (79.3%) out of the 29 Spanish hospitals collaborating with RiHHTa registry and include 1177 HHT patients followed-up by the RiHHTa investigators. Overall, only one patient was admitted for COVID-19 pneumonia. She is a 74 years-old woman with a pathogenic variant in *ACVRL1* gene and hepatic vascular involvement. Her clinical course did not involve mechanical ventilation or worsening epistaxis, and she was successfully discharged after 2 weeks.

This low prevalence of COVID-19 pneumonia among HHT patients may be due to several reasons. First, HHT patients could have self-isolated more strictly than non-HHT patients due to fear of COVID-19 therapeutic measures that might have worsened their recurrent epistaxis. Another possibility could be related to HHT pathogenesis. Observational data on lymphocytic endotheliitis suggest that SARS-CoV-2 provokes endothelial injury [2, 4]. A recent study compared morphologic and molecular features of lungs from COVID-19 patients' autopsy with those who died from influenza and with uninfected controls. The lungs from COVID-19 patients had significant new vessel growth through conventional sprouting and an unexpected mechanism of intussusceptive angiogenesis [2]. In fact, recent evidence has shown higher Vascular Endothelial Growth Factor (VEGF) levels in COVID-19 patients compared with healthy controls [3]. Thus, bevacizumab, a monoclonal antibody against VEGF, is used in an ongoing single-group trial (NCT04275414) in critical COVID-19 patients. Moreover, in a recent study including 99 hospitalized COVID-19 patients, those in the intensive care unit (ICU) had significantly higher circulating

endothelial cells counts than non-ICU patients and were correlated with inflammatory cytokines levels [5]. These findings provide in vivo evidence that the extent of endothelial injury is correlated with disease severity and that endothelial injury is a key feature of COVID-19. Whether or not the HHT pathogenic angiogenesis hinders endothelial damage in COVID-19 deserves further investigation.

Acknowledgements We express our gratitude to Health in Code (A Coruña, Spain) for supporting this Registry.

Author contributions All authors met the required conditions for authorship. ARM conceptualized and designed the study; all authors acquired the data; ARM, AI, MM and RdC analysed the data and interpreted the findings; ARM and DLW contributed to the draft of the manuscript; all authors performed critical revision of the manuscript and approved the final version.

Funding No funding was provided for this study.

Data availability The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

Ethical approval The methodology used in RiHHTa registry was approved by the Clinical Research Ethics Committee of the Hospital Universitari de Bellvitge (Barcelona, Spain; ethic approval number PR241/16). Personal and clinical data that were collected for the study are in line with the Spanish (Organic Law 3/2018) and European (UE 2016/679) Data Protection Regulations.

Informed consent All patients (or their relatives) provided written consent for participation in the RiHHTa registry. To safeguard the identity of the included patients, the RiHHTa registry generate an encrypted identifier for each patient.

Consent for publication Not applicable. This study does not contain any individual person's data in any form. Each patient was identified by a unique alphanumeric identification code and all data were made anonymous and analysed as aggregates.

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References

1. Sánchez-Martínez R, Iriarte A, Mora-Luján JM, Patier JL, López-Wolf D, Ojeda A et al (2020) Current HHT genetic overview in Spain and its phenotypic correlation: data from RiHHTa registry. *Orphanet J Rare Dis* 15:138
2. Ackermann M, Verleden SE, Kuehnel M, Haverich A, Welte T, Laenger F et al (2020) Pulmonary vascular endothelialitis, thrombosis, and angiogenesis in Covid-19. *N Engl J Med* 383:120–128
3. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y et al (2020) Clinical features of patients infected with 2019 novel coronavirus in Wuhan. *China Lancet* 395:497–506
4. Gustafson D, Raju S, Wu R, Ching C, Veitch S, Rathnakumaret K, al, (2019) Overcoming barriers: the endothelium as a linchpin of coronavirus disease 2019 pathogenesis? *Arterioscler Thromb Vasc Biol* 40:1818–1829
5. Guervilly C, Burtey S, Sabatier F, Cauchois R, Lano G, Abdili E et al (2020) Circulating endothelial cells as a marker of endothelial injury in severe COVID-19. *J Infect Dis*. <https://doi.org/10.1093/infdis/jiaa528>

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