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ACE DD polymorphism in severe COVID-19

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Abstract

The insertion/deletion polymorphism of the angiotensin converting enzyme (ACE) gene, previously described in association with adult respiratory distress syndrome, may play a key role in lung injury in patients with SARS-COV2. In this paper we describe 26 patients with severe respiratory failure related to COVID-19 pneumonia that underwent genetic screening for ACE polymorphisms.

Introduction

The insertion (I)/deletion (D) polymorphism of ACE was previously described in association with adult respiratory distress syndrome and correlated with poor outcome [1]. Several studies showed that SARS-COV2 induces lung damage by increasing the permeability of the alveolar-capillary barrier leading to ARDS [2]. ACE is a metallopeptidase that converts angiotensin I to angiotensin II (Ang II), acting as a vasoconstrictor, and it also degrades bradykinin, acting as a vasodilator. ACE2 is a distinct type but a close homologue of ACE; it was identified as aco-receptor for coronaviruses on epithelial lung cells [3]. ACE2 inactivates Ang II and is a negative regulator of the system thus down-regulates the rennin angiotensin system. In a small cohort study, Ang II was remarkably increased in COVID-19 plasma samples [4]. Previous studies reported high Ang II levels in SARS infected mice; in this case Ang II was related to severity of disease, whereas the mice deficient for ACE showed milder disease [5].

Material and methods

We examined 26 patients affected by severe COVID-19, admitted in our intensive care unit between 16 March 2020 and 15 april 2020. 21 were males and 9 females, with mean age 58.5 ± 10.5. At admission, 24 patients had severe respiratory failure with paO2/FiO2<100 mmHg and were treated with mechanical ventilation; 2 patients had mild to moderate respiratory failure with paO2/FiO2>200 mmHg.

The baseline characteristics of patients are described in Table 1. 17 patients (65%) were affected by hypertension. Mean BMI was 28.5 ± 4.5. We tested all patients to assess mutational status of the ACE encoding gene by real time polymerase chain reaction amplification (Table 2).

Results and discussion

26 patients underwent genetics testing. We found that 19 (73%) of our critically ill patients had the D/D polymorphism, 6 (23%) presented I/D polymorphism and only 2 patients (8%) I/I polymorphism.

Delanghe *et al.* recently observed that the prevalence of COVID-19 significantly correlated with ACE D/I polymorphism in 33 countries. At the same time, other polymorphisms, such as complement C3, haptoglobin and vitamin D binding protein, did not show a significant correlation with COVID-19 prevalence [6]. Different studies have associated the D/D genotype with an increased risk of cardiovascular pathologies, due to a consequent increase in the plasma levels of ACE compared to subjects with genotype I/I [7].

Table 1. Baseline Characteristics of critically ill COVID 19 patients

Age (mean ± DS)	58.5 ± 10.5
Male sex *n* (%)	21/26 (81%)
BMI (mean ± DS)	28.5 ± 4.5
Hypertension *n* (%)	17/26 (65%)
Diabetes *n* (%)	4/26 (15%)
Mortality *n* (%)	4 (15%)
Pulmonary Embolism *n* (%)	14/26 (54%)

Table 2. paO2/FiO2 at admission for different ACE polymorphysms. ACE: Gene coding for angiotensin-converting enzyme

	Patients n/%	paO2/FiO2 mmHg
ACE DD	19 (73%)	75,6+/-11,3
ACE ID	6 (23%)	86,9+/-15,3
ACE II	2 (8%)	>200

There is substantial evidence that the ACE I/D polymorphism determines plasmatic ACE concentration, being approximately doubled in individuals with the DD genotype compared to II individuals, with ID individuals having intermediate concentrations. In a recent study, the ACE DD and ID polymorphisms were found to be significantly associated with smoking habits, high plasma ACE levels and high IL-6 levels in STEMI patients [8].

A metanalysis suggests that ACE polymorphisms, particularly the homozygote variant (DD), might contribute to the risk of respiratory disease with pulmonary hypertension [9].

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In several studies, the association between different genes, and not a single one, provide a higher or lower risk of disease, not a single gene [10]. ACE gene I/D polymorphism has also been previously studied in relation to the susceptibility to different diseases with contrasting results. Some authors had described a correlation between ACE polymorphism prevalence and progression of SARS [11]. As the ACE I/D genotype might be involved in the pathogenesis of COVID-19 infection, further studies are required to assess the clinical outcomes of COVID-19 infection in ACE D/D, I/D and I/I carriers and to study the exact role of the ACE polymorphism in COVID-19 infection and its interaction with other polymorphisms.

As literature data are lacking in this scenario, our observation is only preliminary because of the relatively small size of our sample. Further studies should be performed involving a bigger cohort and a control group to better understand the relationship between severity of COVID-19 and different genotypes.

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