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Research Article

Effect of COVID-19 Infection on Serum Diamine-Oxidase Enzyme Concentration

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Abstract

Introduction

Coronavirus infection primarily attack by immune cells, including tissue mast cells, which are found in the submucosa of the respiratory tract and including the nasal cavity. SARS-CoV-2 activates mast cells that release early inflammatory compounds such as histamine and proteases. In those people with diamine-oxidase (DAO) deficiency who, due to this condition, have high levels of circulating histamine, an enhanced histamine accumulation caused by virus-activated mastocytosis, may aggravate the inflammatory process generated by the infection.

Patients and Methods

Three groups were formed; Group 1 consisted of 27 people who were infected before by SARS- CoV-2. Group 2 consisted of 20 "healthy" laboratory workers who had neither been infected nor immunized within the same period. Group 3 consisted of 19 other co-workers who had not been infected but immunized by 2 shots of either BioNTech/Pfizer or Moderna vaccines.

Results

The mean age of patients with COVID-19 infection was 39 years, group 2 was 36.5 years, and group 3 was 50 years. The mean DAO concentration was 11.51 IU/ml in group 1, 15.77 IU/ml in group 2, and 12.35 IU/ml in group 3. Significant difference between group 2 and COVID-19 infected patients serving as controls was in the DAO concentration ($p = 0.013$) was detected.

Conclusion

Patients with COVID-19 infection had significantly lower DAO levels than controls. Vaccinated patients suffering from histamine intolerance tolerated in a worse manner the dose of 2. Vaccine, than those with DAO levels with the reference range. 30 of the 66 patients (45.5%) had DAO concentrations below the reference value. Up till now no similar data was found.

Keywords: Histamine, SARS-CoV-2, DAO, COVID-19 vaccination

Introduction

Histamine intolerance associated with pandemic infection is associated with an overexpression of immune cells. After infection the SARS-CoV-2 virus penetrates the respiratory mucosa, where it binds to epithelial cells in the alveoli. In consequence immune cell activation via pattern recognition receptors has been implicated

as a driver of the hyper inflammatory response seen in COVID-19 [1]. Depending on whether lung mast cell receptors recognize SARS-CoV- 2, or not there will be different activation of mediator release patterns. Mast cells directly recognize SARS-CoV-2 through the ACE2 receptor followed by histamine and proteases release. Activation of mast cells can also be triggered by pathogen-related pathogenic molecular patterns through activation of Toll-like receptors. In this case, degranulation of mast cells does not occur, but de novo production of IL-1 and IL-6 happens. During SARS-CoV-2 infection, mast cell activity induces the release of histamine, proteases, cytokines, chemokine, and prostaglandin D2, as well as leukotriene [2]. Histamine is found in secretory granules, mainly in basophils and mast cells, as well as in gastric enterochromaffin cells, lymph nodes, and the thymus. It amplifies the inflammatory process induced by viral infection, as it enhances IL-1- induced IL-6 gene expression and protein synthesis through H2 receptors in peripheral monocytes. Mast cell activation and histamine release are important for cytokine-driven T- cell differentiation as an adaptive response. Endothelial damage leading to dysfunction is a major burden caused by COVID-19. In this systemic condition the endothelium loses its physiological properties, including tendency to promote vasodilation, fibrinolysis, and inhibition of aggregation. Coagulation disturbance with organ dysfunction and coagulopathy are common in patients with COVID-19. The spike glycoprotein of the SARS-CoV-2 coronavirus reaches the host cell through binding to the enzyme ACE2, sialic acid, Trans membrane serine protease, and the extracellular matrix metalloproteinase inducer [3].

Histamine intolerance may result from an imbalance between accumulated histamine in the body and its impaired ability to eliminate. Degrading enzymes are DAO and N- methyltransferase (NMT), the other important enzyme inactivating histamine, which is a cytosolic protein that can eliminate histamine only in the intracellular space of cells [4]. The vast majority of histamine breakdown occurs extracellular by DAO in the small intestine, ascending colon and kidneys. DAO is a secretory protein that is stored in the vesicular structures of the plasma membrane and is responsible for the degradation of extracellular histamine. Effect of DAO in the gut will also be affected by any inflammation in the intestines. Digestive symptoms are thought to be part of the COVID-19 burden. The incidence of histamine intolerance was 1% in 2007 (4), also in 2015 the prevalence of is estimated 1% at the population has typically presented in people who were middle-aged [5]. Plasma histamine was significantly higher in patients with atopic dermatitis compared with controls groups, reported prevalence of DAO deficiency ranges from 19 to 57% [6].

In people with DAO deficiency who, due to this condition, have high levels of circulating histamine, a greater histamine accumulation caused by the virus-activated mastocytosis, may aggravate the inflammatory process generated by the infection. Decreased DAO activity, in addition to increased histamine, can result in symptoms similar to an "allergic" reaction. See table 1 for symptoms.

Table 1: Symptoms of histamine intolerance.

Organ	Localized or general symptoms
Skin	Itching, "flushing" on the face or anywhere else, wheal angioedema or other figurated exanthems
Gastrointestinal tract	Nausea +/- Vomiting, Diarrhea, Cramps
Heart, Circulation	Tachycardia, Hypotonia, Dizziness
Ears-Nose-Throat	Rhinitis, Nasal Congestion, Sneezing
Nervous System	Headache, Migraine

We observed during the months of pandemic that the serum samples sent to our laboratory to analyze DAO levels produced extremely low values as compared to previous data obtained from the same region. This has prompted us to ask whether any link between mass infection by coronavirus and DAO levels in serum samples existed or not.

Patients and Controls

The studies have been performed using sera of 66 laboratory personnel. All subjects were volunteers and gave their informed written consent to participate in the study. Three groups were formed; Group 1 consisted of 27 people who were infected before by SARS-CoV-2.

Group 2 consisted of 20 "healthy" workers who had neither been infected nor immunized within the same period. Group 3 consisted of 19 our co-workers who had not been infected but immunized by 2 shots of either BioNTech/Pfizer or Moderna vaccines. Their serum was collected at earliest occasion 14 days after the 2 vaccination.

Methods

All sera were frozen -20 ºC. DAO levels from sera were measured using IDK-DAO ELISA (Immundiagnostik AG, Germany). Reference range: 10–100 U/ml. The Seegene Allplex™ 2019-nCoV kit was used for RT-PCR analysis. SARS-CoV-2 spike-specific IgG antibody assay was performed from venous blood on an ABBOTT ARCHITECT analyzer by chemiluminescent microparticle immunoassay (CMIA).

Statistical analyzes were performed with MedCalc Version 20 software (MedCalc Software Ltd., Belgium) and the Mann-Whitney test was used to calculate significance.

Results and Discussion

The results are shown in table 2.

Out of the Group 3 those 8 persons who revealed DAO values below the normal range experienced 24–48 hours after the second vaccination fatigue, malaise and were unable to resume work.

It has to be noted that in 30 of 66 (45.5%) of our colleagues, irrespective to their group DAO levels were detected below of the normal range.

Table 2: Summarized results of our examinations.

Groups and related data	Group I. SARS-CoV-2 infected	Group 2. Controls	Group 3. Non-infected, vaccinated
n	27	20	19
Mean age (yrs.± SD)	39 ± 16	37 ± 17	50 ± 17
male /female	8/19	3/17	1/18
DH below normal range	17/27 63%	5/20 25%	8/19 42%
p value	between 1–2 (0.0134)		between 2–3 (0.2464)

Within the controlled personnel of Hungary's biggest medical diagnostic laboratory – network the serum levels of the histamine-degrading DAO enzyme were below the normal range depending on the fact of acquisition SARS-CoV-2 infection. This phenomenon could be detected also within the non-infected but vaccinated subgroup of otherwise healthy subjects. The vaccination induced adverse events were related to the low DAO levels. Following COVID-19 infection, the DAO concentration of colleagues suffering from histamine intolerance decreased to a greater extent, than those co-workers, who have no histamine intolerance. No similar data in the literature was found.

Author contributions

E. P. as the main author conceived the research collected the data, M. K. participated in writing of the manuscript, K.L. provided virus examinations, J. M B-B revised the final version of the manuscript. All authors contributed to the writing and approved the final manuscript.

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