Reactivation of Herpes Human Viruses During SARS-CoV-2 Mild Infection

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BACKGROUND

Human Herpes Viruses (HHV) are a family of DNA viruses, representing a class of the most common infectious pathogens for humans. Almost 100% of the adult population in the world is infected with at least one HHV during their life. All HHV can establish latent infection within specific tissues, which are characteristic for each virus (1). Reactivation of HHV has been described mostly in severe SARS-CoV-2 patients (2). HHV co-infection may affect disease severity in terms of clinical manifestations, prolonging the illness course, and potentially triggering post COVID syndrome (3). The aim of our study was to investigate the HHV reactivation, HHV-mediated T-cell response and inflammatory milieu during SARS-CoV-2-mild infection.

METHODS

The assessment of HHV reactivation ,T-cells specific response and inflammatory background in SARS-CoV-2 infected patients and in healthy donors (HD) was performed at baseline, day 7 and day 30. It has been evaluated: HHV-serology in enzymatic test, HHV-DNA-plasma level with PCR, IFN-γ production after stimulation with HHV peptides and plasma cytokine levels (IL-2, IL-6, IL-8, TNF-α, IFN-γ, CXCL-10) by an automated Elisa test.

Clinical features of COVID-19 pts and HD

Table 1 Clinical features

		COVID+ (60 pts)	HD (pts 20)	p-value
SEX F		29 (48%)	12 (60%)	
AGE, median (IQR)		61 (50 - 70)	62 (55,5 - 76)	NS
BMI, median (IQR)		25,4 (23,6 - 28,9)	25,2 (21,9 - 29,3)	NS
VACCINE (2 OR MORE), n(%)		57 (95%)	15 (75%)	0.001
COMORBITIDIES, n(%)	DIABETS/CCV diseases	9 (15%)/20(33%)	1 (5%)/1(5%)	
	CANCER/HAEMATOLOGICAL diseases	19 (31%)	0	
	IMMUNODEFICIENCY Primary/Secondary	12 (20%)/9(15%)	0/0	
	PULMONARY diseases/RENAL failure/BMI>30	10 (16%)/5(8%)/14(23%)	0/1(5%)/ 5(25%)	
CHARLSON INDEX		12	4	

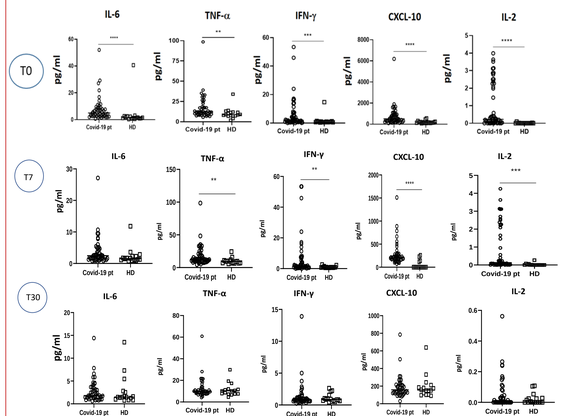
Table 2. Laboratory tests

		COVID+ pts 60	HD pts 20	p-value
SIEROLOGY, IgG n° of pts	HSV-1 +/HSV-2 +	44 (73%)/6 (10%)	17 (84,2%)/1(5%)	NS
	CMV +	48 (80%)	18 (90%)	NS
	EBV +	50 (91%)	19 (95%)	NS
	VZV +	53 (88%)	19 (95%)	NS
	SARS-COV-2 ANTI S +	51 (85%)	19 (95%)	NS
DNA PRESENCE				
T0, T7, T30 n° of pts (%)	HSV-1/2	0 - 0 - 0	0 - 0 - 0	
	VZV	1 (1,6%)- 0 - 0	1 (5%) - 0 – 0	NS
	CMV	3 (5%) – 1 (1,6%) – 2 (3,2%)	0 - 0 - 1 (5%)	NS
	EBV	15 (25%) - 18 (30%) - 13 (21%)	7 (35%) - 7 (35%) - 5 (25%)	NS

At T0, no difference in lymphocytes count (while CD3 and CD4 T cells differed both with a p<0.0001), in HHV-seroprevalences, HHV-antibodies level and HHV reactivation were reported between groups. Blood EBV-DNA was most commonly detected at T0-T7-T30 in COVID pts, with no difference between groups.

Reactivation of HHV During SARS-CoV-2 Mild Infection may be a tool to understand possible post-sequelae

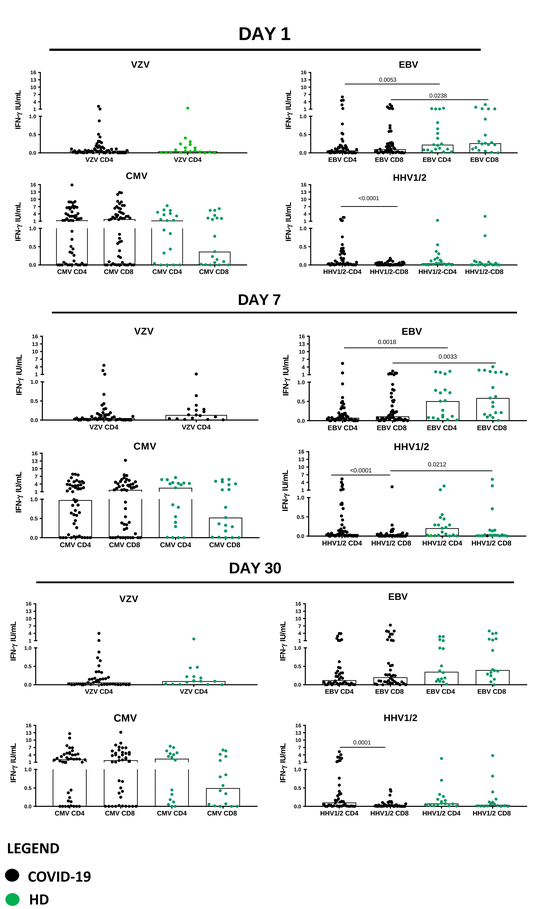
RESULTS 1. Cytokines plasma level in COVID-19 pts and HD at baseline and after 7 and 30 days



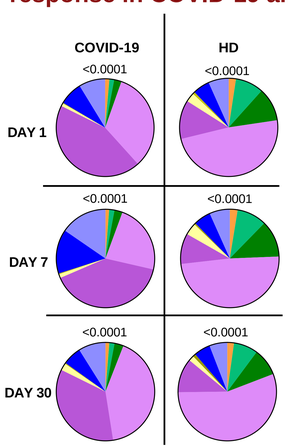
At T0, all cytokines were significantly higher than HD maintaining their high expression at 7 days also. After 30 days their values reached healthy donors. Test Mann Whitney; ****p<0,0001; ***p<0,001; **p<0,007.

RESULTS 2. Specific T-cell response to HHV in COVID-19 pts and HD at baseline, and after 7 and 30 days.

Antigen of specific T-cell response to HHV peptides in COVID-19 pts and HD at baseline and after 7 and 30 days. Read out: IFN-γ production after overnight stimulation.



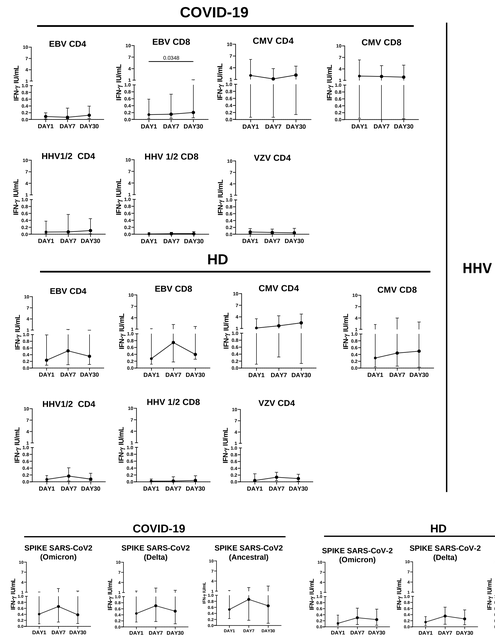
RESULTS 3. High magnitude of CMV specific response in COVID-19 and HD



Proportion of specific T-cell response to HHV and SARS-CoV-2 peptides in COVID-19 pts and HD at baseline and after 7 and 30 days was analyzed. Read out: IFN-γ production after overnight stimulation.

RESULTS 4 Comparison of specific T-cell response to HHV in COVID-19 pts and HD at baseline and after 7 and 30 days.

Antigen of specific T-cell response to HHV and SARS-CoV-2 peptides in COVID-19 pts and HD at baseline and after 7 and 30 days. Read out: IFN-γ production after overnight stimulation.



CONCLUSIONS

- **Our findings indicate an inflammatory environment and heightened HHV T-cell response in mild SARS-CoV-2 infection. Although the inflammatory environment resolves by day 30, the alteration of HHV-T cell response persists overtime.**
- **The notable CMV response suggests its potential involvement in immune modulation during SARS-CoV-2 infection.**
- **The potential of subclinical HHV reactivation during mild SARS- CoV-2 infection warrants further investigations.**

References:

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