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Case Report

Immunogenetic Studies and Humoral Reactivity in an Affected COVID-19 First Wave Family

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Introduction

The Covid-19 pandemic has been divided into different infection periods (waves) [1]. The first wave started in Europe mid-January 2020 and was characterized initially by dedicated hotspots of infections, from which the virus spread to the general population [2]. The second and the possibly third wave are characterized by viral mutations and possible increased virulence. Even during the first wave mutations like the spike gene D614G with higher infectiousness evolved [3]. Earlier it was stated that blood group O might be to a certain degree protective against SARS-CoV-2 infection or at least protects from a severe course of COVID-19 [4]. We started a local cooperative study on the influence of immunogenetic factors on disease occurrence, spreading, and severity. Here, we report on HLA, blood group, and humoral antiviral immunity data of a SARS-CoV-2-infected family during the first wave of the pandemic disease.

Material and Methods

Our laboratory is accredited for the PCR technology and antibody detection by Luminex technology by the European Federation for Immunogenetics and participated successfully in several external proficiency testing exercises on HLA typing by Next Generation Sequencing (NGS). Regarding this technology we used the AlloSeq® Tx 17 from CareDx, San Fransisco, CA, USA, for HLA typing. The sequencing was performed on Miseq from Illumina (San Diego, CA, USA), following strictly the manufactures recommendations. Alternatively Real Time PCR was used. In addition to the "classical" loci HLA-A, B, C, DRB1, DRB3, DRB4, DRB5 DQA1, DQB1, DPA1 and DPB1, also typed for HLA-E, HLA-F, HLA-G, HLA-H, MICA and MICB. The results of HLA-F and H were not informative and therefore not reported here.

ABO and Rh typing were performed using the PCR sequence specific priming for blood groups of BAG, Lich, Germany, following the manufactures recommendations.

The LAB Screen™ COVID Plus assay is Luminex® based from One Lambda, West Hills CA, USA. It was strictly followed the manufactures recommendations and used the proposed cutoff values as given by the manufacturer to quote a given value as positive or negative. The assay consists of antigenic determinants bound to polystyrene beads and used in the Luminex® set up (LX200, IS 2.3). The assay detects simultaneously the presence of 5 different SARS-CoV-2 targets and 6 additional coronavirus targets for antibodies present in the subject serum (modified from One Lambda (https://www.onelamdba.com)).

Table 1: Antibody targets in the assay.

Target	Description
SARS-CoV-2 Spike	Extra Cellular Domain (ECD)
SARS-CoV-2 SpikeS1	S1 Domain
SARS-CoV-2 Spike RBD	Receptor Binding Domain
SARS-CoV-2 SpikeS2	S2 Domain
SARS-CoV-2 Nucleocapsid Protein	Nucleocapsid Protein
HCOV-229E Spike S1	Common Cold Human Coronavirus 229E
HCoV-HKUl SpikeS1	Common Cold Human Coronavirus Hong Kong Ul
HCOV-NL63 Spike S1	Common Cold Human Coronavirus Netherland 63
HCOV-OC43 Spike S1	Common Cold Human Coronavirus Organ Culture43
MERS-CoV Spike S1	Middle East Respiratory Syndrome Coronavirus
SARS-CoV Spike S1	Severe Acute Respiratory Syndroma Coronavirus (2003)

The study was accepted by the ethical committee of our hospital (195/20e-ek). After detailed explanation of the study and investigation the agreement of the family´s legal guardians was obtained by signing the informed consent. For the study, EDTA and serum samples were taken according to the study documents (provided as supplemental material) in case of need.

Results

Family LEI-01:

The family consists of the mother (M), her two daughters (C1, 16 years old and C2, 13 years old) from a previous partnership, her current partner (F2 and a mutual daughter (F2M C1, 17 months). All members of the family were tested by SARS-CoV2 PCR assay according to WHO standards (https://www.WHO.int; https://www.ecdc.europa.eu/en/covid-19/latest-evidence/diagnostic-testing). All were positive with exception of C1. All family members were admitted to the hospital. F2 had severe respiratory problems with fever and oxygen was administrated. M had mild cold symptoms with pneumonia but no fever. C2 had mild fever and cold symptoms, while C1 and F2M C1 were asymptomatic (Table 2). NB the family shares housing. HLA and blood group typing were performed by molecular means. In addition, a novel Covid antibody assay was used, in which five SARS-CoV2 specific antigens was included as targets for the antibodies, and six additional human specific antigens of other coronavirus than SARS-CoV2 were used in parallel (Table 1).

The results of the HLA typing of the family are depicted in Table 3. The HLA haplotypes of the first partner of the mother are deduced. The F2M C1 child was typed for HLA-A, B, C, DRB1 and DQB1 in 1-field resolution. The remaining results were deduced from the inherited haplotype C from M and E from F2. No sharing of haplotypes was observed. However, since the C1 and C2 daughters inherited different haplotypes from the mother one could speculate that an immunogenetic component might influence the severity of the Covid-19 infection. The asymptomatic F2M C1 child inherited the same haplotype as the C1 and could represent a protective haplotype.

We also performed the definition of the blood groups by sequence specific priming PCR, with exception of F2 and M. Their typing was done by usual serological manner. The results are shown in Table 4. Blood group O was shown to be rather protective towards SARS-CoV2 [4]. Since all members of the family are BG O no conclusions are drawn.

Table 2: Symptoms of family members who have Covid-19.

	F2	M	F2M C1	C2
duration of symptoms	10 days	14 days	no*	1 day
fever	yes, max. 39,5°C	no	no*	yes, 38°C
headache	yes	yes	no*	not known
body aches	yes	yes	no*	not known
tiredness	yes	yes	no*	not known
cough	yes	no	no*	not known
runny nose	no	yes	no*	not known
hoarseness	no	no	no*	not known
sore throat	no	no	no*	not known
pneumonia	yes	yes	no*	not known
sinus discomfort	no	no	no*	not known
dizziness	no	no	no*	not known
taste/smell disorders	yes, since day 4 until January 2021	yes	no*	yes, lightly
depressive moods	no	no	no*	not known
skin redness	no	no	no*	not known
skin vesicles	no	no	no*	not known
nausea/vomiting	no	no	no*	not known
abdominal pain	no	no	no*	not known
diarrhea	yes	no	no*	not known
constipation	no	no	no*	not known
hair loss	yes	yes	no*	not known
Hospitalized, hospital days	yes/16 days	yes/not known**	yes/not known**	not known
oxygen supply	yes, 2l/min	no	no*	not known
Invasive/non-invasive ventilation	no	no	no*	not known
medication for treatment during infection	not known	not known	none	not known
long-term medication	none	Cardesartan	none	not known
other	fungal infection	hip pain, increased blood pressure, myocarditis	no*	not known

*observations of the parents; **no treatment needed

Table 3: HLA typing of the family LEI-01.

			HLA													MIC	
	SARS CoV2 PCR	HLA-Haplotype	A*	B*	C*	DPA1*	DPB1*	DQA1*	DQB1*	DRB1*	DRB3*	DRB4*	DRB5*	E*	G*	A*	B*
F Deduced	nt	A	01:01:01	40:02:01	02:02:02	01:03:01	03:01:01	04:01:01	04:02:01	08:01:01		01:01:01		01:03:02	01:06:01	027:01	013:01
		B	03:01:01	15:01:01	03:04:01	01:03:01	04:01:01	03:01:01	03:02:01	04:01:01		01:03:01		01:03:02	01:01:01	010:01	002:01
M	positve	C	23:01:01	44:03:01	04:01:01	01:03:01	03:01:01	02:01:01	02:02:01	07:01:01		01:01:01		01:01:01	01:04:04	004:01	005:02
		D	02:01:01	13:02:01	06:02:01	01:03:01	04:01:01	03:03:01	03:01:01	04:01:01		01:03:01		01:03:02	01:01:01	008:01	005:02
C1	negative	A	01:01:01	40:02:01	02:02:02	01:03:01	03:01:01	04:01:01	04:02:01	08:01:01		01:01:01		01:03:02	01:06:01	027:01	013:01
		C	23:01:01	44:03:01	04:01:01	01:03:01	03:01:01	02:01:01	02:02:01	07:01:01		01:01:01		01:01:01	01:04:04	004:01	005:02
C2	positve	B	03:01:01	15:01:01	03:04:01	01:03:01	04:01:01	03:01:01	03:02:01	04:01:01		01:03:01		01:03:02	01:01:01	010:01	002:01
		D	02:01:01	13:02:01	06:02:01	01:03:01	04:01:01	03:03:01	03:01:01	04:01:01		01:03:01		01:03:02	01:01:01	008:01	005:02
F2	positve	E	03:01:01	07:02:01	07:02:01	01:03:01	04:01:01	01:02:01	06:02:01	15:01:01			01:01:01	01:01:01	01:01:01	008:04	002:01
		F	25:01:01	18:01:01	12:03:01	01:03:01	04:01:01	05:05:01	03:01:01	11:04:01	02:02:01			01:03:02	01:01:02	018:01	004:01
F2MC1	positive	E	03:01:01	07:02:01	07:02:01	01:03:01	04:01:01	01:02:01	06:02:01	15:01:01			01:01:01	nt	nt	nt	nt
		C	23:01:01	44:03:01	04:01:01	01:03:01	03:01:01	02:01:01	02:02:01	07:01:01		01:01:01		nt	nt	nt	nt

Table 4: ABO and Rh typing of the family.

	SARS CoV2 PCR	ABO		RH
F2	Positive	0	nd	CcDEe
M	Positive	0	nd	CCDee
F2M Cl	Positive	0^{1}	0^{1v}	CcDDEe
Cl	Negative	0^{1}	0^{1v}	CCDDee
C2	Positive	0^{1}	0^{1v}	CCDDee

Finally, the reactivity of the serum antibodies towards the different SARS-CoV-2 antigens and those from epidemic coronaviruses were analyzed. The results are shown in Table 5.

Table 5: Antibody reactivity towards SARS-CoV2 and other coronavirus antigens (shaded boxes indicate positive results).

	Sample date		SARS CoV2 antigens					Other coronavirus antigens					
	SARS-Cov2 PCR	Covid Plus antibody	SARS-CoV-2 Spike	SARS-CoV-2 Spike S1	SARS-CoV-2 Spike RBD	SARS-CoV-2 Spike S2	SARS-CoV-2 Nucleocapsid Protein	HCoV-229E Spike S1	HCoV-HKU1 Spike S1	HCoV-NL63 Spike S1	HCoV-OC43 Spike S1	MERS-CoV Spike S1	SARS-CoV Spike S1
F2	05.04.2020 pos 29.04.2020 neg	16.10.20											
M	01.04.2020 pos	16.10.20											
F2MC1	16.04.2020 pos	25.01.21											
C1	15.04.2020 neg 16.04.2020 neg 26.04.2020 neg	16.10.20											
C2	15.04.2020 pos 26.04.2020 pos 27.04.2020 pos	16.10.20											

All members of the family with exception of the C1 showed positive reactions against all five SARS-CoV2 targets. Because of the negative PCR assay, a negative antibody assay for C1 is plausible.

Discussion

The family LEI-01 came to our Institution to participate in our local cooperative study. The members of this family live together and are prone to cluster infections like COVID-19. The C1 individual had no infection as proven by negative PCR and lack of antibodies against the SARS-CoV-2 while antibodies

against epidemic coronaviruses were detected. M and the F2M C1 child had mild symptoms or no symptoms at all. The mother was PCR positive and developed antibodies against several SARS-CoV-2 antigens, as also her F2M C1 offspring. The latter had no symptoms.

Very little is known with regard to SARS-CoV-2 infection and the Major Histocompatibility Complex [5–7]. It is far too early to define immunogenetic factors in the family presented where the respective individuals had varying degrees of symptoms. However, because of the different affected HLA haplotypes one could speculate that the haplotype inherited from the mother to the C1 child might include a protective factor. These three individuals express the haplotype C including the HLA-A*23:01, B*44:03, C*04:01, DRB1*07:01, DQA1*02:01, DQB1*02:02. We can speculate that this haplotype protects in a way the carriers from SARS-CoV2 infections and severity. Further analyses in a wider patient population will show whether this assumption is correct.

Acknowledgement

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