Hebron University Research Journal-A (Natural Sciences) - (مجلة جامعة الخليل للبحوث- أ (العلوم الطبيعيه)

Volume 10 | Issue 1 Article 5

2021

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Hebron University Research Journal (B)
Vol.(10), pp.(75-91), 2021

H.U.R.J. is available online at
http://www.hebron.edu/journal

ABO blood groups and COVID-19 transmission among family members living in the same household

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Received: 29/9/2021- Accepted: 30/12/2021

Abstract:

Background: ABO blood groups may play a major role in the way COVID-19 spreads among same family members.

Objective: To determine the trends in the spread of COVID-19 in families according to their ABO blood groups. Explore the interrelationships between the main symptoms of COVID-19 infection.

Results: Two hundred forty-four subjects exposed to the SARS-CoV-2 virus participated in this study, 52 % males, age 29.64 ± 18.78 years. Forty-four percent of subjects have blood group A, 9 % were B, 7 % were AB and 32 % were O. Thirty-eight percent of polymerase chain reaction (PCR) positive subjects have blood group A and 37 % have blood group O. There was a significant association between the blood group of family members and the transmission of COVID-19, $p < 0.05$.

There was also a significant relationship between the loss of taste, smell or both senses and anorexia, $p < 0.05$. Headache was the most common symptom; 63 % of symptomatic patients who responded to this question.

Conclusion: COVID-19 transmission among family members may follow the blood transfusion compatibility model.

Key words: COVID-19, transmission, ABO blood groups, index family member, PCR.

فصائل الدم ABO وعلاقتها بانتقال عدوى كوفيد تسعة عشر بين افراد الاسرة الذين يعيشون في نفس المنزل

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تاريخ الاستلام: 2021/9/29- تاريخ القبول: 2021/12/30

الملخص:

قد تلعب فصائل الدم دوراً رئيسيا في انتقال عدوى كوفيد 19 بين افراد الأسرة أنفسهم والذين يعيشون في نفس المنزل. ولذلك هفت هذه الدراسة لتحديد اتجاهات انتشار عدوى كوفيد 19 في العائلات وفقا لفصائل الدم واستكشاف العلاقات المتبادلة للأعراض الرئيسية للمرض. شارك 244 شخص في هذه الدراسة ممن تعرضوا للفيروس،52% ذكور، معدل اعمارهم 18.78 ±29.64 عاماً. أظهرت النتائج أن أربعة واربعون بالمائة منهم لديهم فصيلة دم أ، 9% كانوا ب، 7% أب، و32% كانوا و، ثمانية وثلاثون بالمائة من الذين جاء فحصهم ايجابي باستخدام تفاعل البوليميراز المتسلسل كانت فصيلة الدم لديهم (أ) و 37% فصيلة دمهم (و)، كان هناك ارتباط كبير بين فصيلة الدم لافراد الاسرة وانتقال كوفيد 19 حيث الدالة الاحصائية كانت اقل من 0.05، كما توجد علاقة معنوية بين فقدان حاستي التذوق والشم وفقدان الشهية بدالة احصائية اقل من 0.05، كان الصداع أكثر الأعراض شيوعًا(63٪) بين المرضى الذين عانوا من الأعراض و الذين أجابوا على هذا السؤال.

الخلاصة: قد يتبع انتقال كوفيد 19 بين افراد الاسرة نموذج توافق نقل الدم بين الاشخاص.

الكلمات المفتاحية: كوفيد 19 ،انتقال العدوى، فصائل الدم (أ،ب،و)، مريض صفر في العائلة، تفاعل البوليمرايز المتسلسل **PCR.**

Introduction:

COVID-19, a pandemic infectious disease with high mortality, has spread quickly from Wuhan, Hubie Province, China, to nation wide [1]. Human-to-human transmission is occurring among close contacts since December 2019 [2]. The virus is found in droplets and respiratory secretions of infected persons and in fecal swabs of severe pneumonia COIVD -19 patients[3]. The mystery of COVID-19 spreading among individuals at the same community and how it affects only certain individuals of the community, is still unraveled. Why some people suffer from severe symptoms while others suffer from mild symptoms or no symptoms at all is also a mystery? Why are some members of the same household who are confirmed as carrier contacts not afflicted with the virus at all? These questions, along with many others, about severity of symptoms, mode of transmission, cellular receptors, and entrance for the virus, genetic predisposition for a higher risk of infection, or death from infection have not answered yet.

SARS-CoV-2 is an enveloped non-segmented positive sense RNA virus [3], which is characterized by a heterogeneous clinical course. Patients showed a wide range of symptoms; from mild, to moderate, or severe symptoms**.** Although most SARS-CoV-2 infections are not severe, a significant percentage of patients required hospitalization and many deaths occurred. Increased rates of severe and fatal versions of SARS-CoV-2 infection (respiratory distress, respiratory failure, multiple organ failure and even death in some cases) were observed among older individuals (>65 years) and those with preexisting medical conditions such as cardiovascular disease, obesity, and type 2 diabetes mellitus [4]**.**

ACE-2 is an aminopeptidase that converts Angiotensin-II to Angiotensin (1-7). Angiotensin- converting enzyme-2 receptors (ACE-2 R), serve as a binding site for the virus in host cells [5].

A large number of studies investigated the expression of the ACE-2 gene in human tissues. It was expressed in the heart, kidneys, gastrointestinal tract (GIT), lungs, brain, testes, bladder, adipose tissue, and vascular system. In a recent

study, ACE-2 was detected in cholangiocytes and epithelial cells of the oral and nasal mucosa [6].

The ABO blood group was reported to be associated with classical ACE activity. It was also associated with the antihypertensive drug family (ACE inhibitors)-induced cough among Chinese patients with essential hypertension. That is, the GATC haplotype of the four polymorphisms of the ABO gene (*rs8176746, rs8176740, rs495828, rs12683493),* which is prevalent among patients with non-O blood type, is positively associated with ACE activity.

This implies that blood type O carriers have lower levels of ACE and a higher probability of enjoying protection specifically from ACE-2-conveyed benefits. Accordingly, blood type O carriers have a higher level of interleukin 6 (IL-6). As a pro-inflammatory cytokine, IL-6 triggers the production of acute-phase proteins such as C-reactive protein. Higher levels of C-reactive protein were detected among ACE-inhibitor-induced coughers than in controls was found among participants in this study [7]. In another study, the ABO phenotype was shown to be a valid predictor of ACE activity [8].

The level of IL-6 is correlated with the degree of faintly morbidity and mortality especially with respiratory impairment [9]. It was already shown that understanding the details of inflammatory and clinical aspects of IL-6 may help to study COVID-19 virus. IL-6 level could be affected with these factors; age, low-calorie diet and exercise [10], sex differences [11], obesity, diet, and lifestyle. In lieu, dexamethasone and Vitamin D can suppress IL-6 expression, which partially accounts for their anti-inflammatory effects [12]. Experimental evidence showed that IL-6 overexpression during viral immune response could induce viral persistence by altering TH1 cells polarization and functionality and the lytic capacity of CD8 t-cells through different mechanism, leading to chronic infection, induces viral persistence [13].

The ABO blood group is the most important blood group system in humans and includes 4 blood types, namely A, AB, B, and O. The GEWAS group identified a *3p21.31* gene cluster as a genetic susceptibility locus in patients with COVID-19

with respiratory failure and confirmed a possible involvement of the blood-group system ABO [14], since ABO is located on chromosome 9 (*9q34.2*).

A plethora of studies have found ABO blood group plays an important role in various human diseases, such as cardiovascular, oncological, and some infectious and non-infectious diseases. Meanwhile, the system can play a direct role in infection by serving as receptors or coreceptors for microorganisms, parasites, and viruses. ABO is related to hepatitis B, Rota positive status for rotavirus gastroenteritis, malaria, and dengue virus. The association between ABO blood type and lymphocyte count was also investigated. Lymphopenia in COVID-19 was a critical factor associated with the severity and mortality of the disease [15].

However, too many genetic factors (ICAM1 system, PBDX gene encodes for XG antigen in RBC) related to a highly contagious widely spread COVID-19 infection, patients with symptoms ranging in intensity and severity from common flu and cold symptoms such as cough, fever, dyspnea, musculoskeletal symptoms (myalgia, joint pain, fatigue), gastrointestinal symptoms, and anosmia/dysgeusia to severe respiratory distress and death are found worldwide. However, information on symptoms that persist after recovery is lacking [16]. Headache has also been established to be a common symptom in patients with coronavirus disease [17].

In this study, we are exploring for the first time the effect of the ABO blood group of infected index family member on the transmission of COVID-19 to other members of the family according to their blood groups, which were confirmed to be in close contact with the index member at time and place.

This might help prevent the transmission of the disease by avoiding contact with COVID-19 carriers or infected patients with blood groups that are known to be highly contagious.

Materials and methods:

This is a retrospective cohort study of family members who were exposed to SARS-CoV-2 virus infection with an identified index family member and a clear chain of infection who lived in the same household. Subjects were classified

according to the results of the polymerase chain reaction (PCR) test as follows; 57 subjects as the index family members (PCR positive), 101 subjects as contact family members (PCR positive), and 86 subjects as carrier contacts who were not tested and did not show symptoms. Subjects who showed symptomatic but were not PCR-tested, were excluded from the study. We confirmed the spread of infection by precisely following the clear chain of transmission, the incubation period, and appearance of symptoms among family members who were in close contact with index family member. We only included family members who live together and excluded family members who are not living in the same household or contracted the infection while not in contact with the index family member. All subjects included in this study were tested after the appearance of symptoms.

Sociodemographic and clinical data were collected by personal interview on the mobile or web-based apps from September to December 2020. Data analysis was done using SPSS version 23.

Results:

Our sample consisted mainly of young subjects; however age wasn`t related to transmission of COVID-19, rather it was associated with the prevalence of infection. Almost 50% of the older subjects (60 years and up) family members were PCR positive, and approximately 70% of 41-50 years were positive too, whereas the very young (5 and under) were less likely to be positive. The socio demographic and clinical data of the study sample are shown in Table 1.

Headache was the most frequent symptom (63 %) of symptomatic patients who responded to this question, followed by anorexia (52%), loss of taste and smell (51%), GI symptoms (44%), then dizziness (30%) (Table 2).

Using the Fischer exact test, there was a significant relationship between COVID-19 and ABO blood groups of the index family member and blood groups of infected contacts, $p = 0.00$, (Table 3).

We also found that 84.6 % of all subjects that contracted the infection from index family member with blood group, A have blood group A too. In the same way, 53.8 % with blood group, O got infected from index family member with blood

group O, (Table 3). In the same table, we noticed that 22 patients with blood group A out of a total of 44 contacts with blood group, A contracted the infection from index family member with blood group A, almost 50% of the sample.

We elaborate on loss of appetite as the main annoying symptom among our patients and its relation to other symptoms. We found that loss of smell and taste was closely related to and significantly affected anorexia, p = 0.00, (Table 4).

Table 1: Sociodemographic and clinical data from COVID-19 patients

Variables	**Index patient (PCR positive) (N=57)**	***Family members (N=187)**	**PCR positive contacts (N=101)**
	N (%)	**N (%)**	**N(%)**
Blood group			
A	15 (27.8)	93 (54.1)	46 (50)
B	11 (20.4)	12 (7)	6 (6.5)
AB	4 (7.4)	13 (7.6)	6 (6.5)
O	24 (44.4)	54 (31.4)	34 (37)
Total	54 (100)	172 (100)	92 (100)
Age			
0-5	0 (0)	17 (9.1)	2 (2)
6-17	7 (12.3)	56 (29.9)	30 (29.7)
18-30	11 (19.3)	53 (28.3)	31 (30.7)
31-40	5 (8.8)	15 (8)	9 (8.9)
41-50	17 (29.8)	24 (12.8)	17 (16.8)
51-60	10 (17.5)	16 (8.6)	9 (8.9)
More than 60	7 (12.3)	6 (3.2)	3 (3)
Total	57 (100)	187 (100)	101 (100)
Gender			
Male	29 (50.9)	99 (52.9)	56 (55.4)
Female	28 (49.1)	88 (47.1)	45 (44.6)
Total	57 (100)	187 (100)	101 (100)

*All family members whether they were tested, positive or negative on PCR, had no test at all, or had no symptoms, but were in contact with the index family member.

Table 2: Distribution of symptoms among symptomatic COVID-19 subjects of the study

Symptoms	**Index patient (N=57)**	**PCR positive Contacts (N=101)**
Headache		
Yes	43 (76.8)	56 (55.4)
No	13 (23.2)	45 (44.6)
Total	**56 (100)**	101 (100)
Loss of taste and smell		
NON of them	14 (31.8)	33 (35.1)
Aguesia	2 (4.5)	7 (7.40)
Anosmia	3 (6.8)	8 (8.5)
BOTH	25 (56.8)	46 (48.9)
Total	**44 (100)**	94 (100)
Dizziness		
yes	15 (30)	25 (31.3)
No	35 (70)	55 (68.8)
Total	**50 (100)**	80 (100)
Anorexia		
yes	26 (52)	43 (52.4)
No	24 (48)	39 (47.6)
Total	**50 (100)**	82 (100)
GIT symptoms		
Yes	29 (53.7)	36 (38.3)
No	25 (46.3)	58 (61.7)
Total	54 (100)	94 (100)

Cells represent frequency (valid percent)

Table 3: Relationship between the blood groups of index family member and other family members (whether infected, uninfected, or not tested) and the transmission of COVID-19.

		Blood group of index family member				Test value	Sig.
		A	B	AB	O		
Infected	A	22 (84.6)	6 (28.6)	2 (66.7)	15 (39.5)	27.113	0.00
	B	0 (0)	3 (14.3)	0 (0)	2 (5.1)		
	AB	0 (0)	3 (14.3)	1 (33.3)	1 (2.6)		
	O	4 (15.4)	9 (42.8)	0 (0)	21 (53.8)		
	Total	26 (100)	21 (100)	3 (100)	39 (100)		
Uninfected	A	13 (86.7)	0 (0)	0 (0)	13 (59.1)	23.448	0.00
	B	0 (0)	2 (40)	0 (0)	1 (4.5)		
	AB	0 (0)	3 (60)	0 (0)	0 (0)		
	O	2 (13.3)	0 (0)	0 (0)	8 (36.4)		
	Total	15 (100)	5 (100)	0 (0)	22 (100)		
No symptoms, not test	A	9 (90)	2 (28.6)	0 (0)	6 (46.1)	14.87	0.03
	B	0 (0)	1 (14.3)	1 (25)	1 (7.7)		
	AB	0 (0)	1 (14.3)	2 (50)	1 (7.7)		
	O	1 (10)	3 (42.8)	1 (25)	5 (38.5)		
	Total	10 (100)	7 (100)	4 (100)	13(100)		
All sample	A	44 (86.3)	8 (24.2)	2 (28.6)	34 (45.95)	57.91	0.00
	B	0 (0)	6 (18.2)	1 (14.3)	4 (5.4)		
	AB	0 (0)	7 (21.2)	3 (42.8)	2 (2.7)		
	O	7 (13.7)	12(36.4)	1 (14.3)	34 (45.95)		
	Total	51 (100)	33 (100)	7 (100)	74 (100)		

Table 4: Relationship between COVID-19 symptoms and loss of appetite among symptomatic patients.

						Test value	Sig.
Loss of appetite	**Didn't lose smell or taste**	**Ageusia**	**Anosmia**	**Loss of both senses**	**Total**		
Yes	5 (12.5)	5 (12.5)	6 (15)	24 (60)	40 (100)	17.519	0.00
No	20 (52.6)	0 (0)	2 (5.3)	16 (42.1)	38 (100)		

Cell represents: counts (percent). Fisher exact test

Discussion:

In a close conservative community with a family-based in structure with extended families and close social relationships, it is worth studying the influences and risks of the transmission of COVID-19 among its members.

Having a quick glance at our results, it was obvious that family played a major role in acquiring, retaining, and spreading the infection. Adding to that, Palestine is a semi-isolated country, because of many restrictions of traveling and prohibiting traveling even in between cities since then.

Our results showed a direct relationship between the blood group of index family member and the transmission of COVID-19 infection to other family members according to their blood group. The members of the blood group O in the family contracted the infection mainly from an index family member with the blood group O.

A study that addressed the same issue for a group of people in the aircraft found no relation between blood group and transmission of COVID-19 which contradicted our findings [18]. However, this study is best representative of the proximity and duration of exposure rather than the relationship between ABO blood group and COVID-19 transmission. First of all, these people are not blood relatives. It is not only the blood group but also the nature and location of the XG antigen on the short arm of the X chromosome that might play an unknown role

yet in transmission of infection. Second, the probability of having a close genetic background of same family members for the ABO blood group and XG loci is greater than that for nonrelated passengers on an aircraft. These similarities in genetics of the same family members might present a similar entrance or similar host immune-system-virus interaction that facilitates viral transmission [19].

In an analysis of data stratified by spouses who were husbands or wives of index cases, demonstrated that the secondary attack rate of SARS-CoV-2 to spouses was significantly higher than that to other family members. This could be explained on the basis of a longer exposure time and the greater chance of contacting disease between spouses comparing to exposure time of other family members within the same household [20]. This study supports our findings first hand, and, on the other hand, it proves our suggestions that the results of the above aircraft study were due to proximity only.

Another study by Somekh E. et al., about closely-related crowded city of Bnei-Brak, found that children aged 5-17 years were 61% and children aged 0-4 years were 47% less likely to have positive polymerase chain reaction results compared to adults residing in the same household [21]. In our study, a small percentage of exposed children were tested positive.

The distribution of blood groups in Palestine was found to be intermediate between those of the West and the Far East. It follows the same overall trends where the blood group A predominates, followed by O, then B and finally AB. In other words, blood group A forms the highest percentage in Palestine, and blood group, AB is the least [22]. This matched the results of our study where we had almost the same percentage of blood groups in our sample.

The frequency of ABO for both sexes can be shown with a general formula A>O>B>AB, this study was carried at Al-Azhar University, Gaza, Palestine [23]. Consequently, the results of our study could be applicable to other countries in relation to blood group A with limitations for blood group AB. Subjects in our study are mainly healthy young people living at same household. This shows the increased risk of COVID-19 transmission among closely-related family members living in the same household (eating together, share towels, living rooms, dining

rooms, bed rooms and bathrooms) with blood group A being the main contributor, than blood group O.

Having blood group A as dominant blood group in Palestine, it was not surprising to be the main blood group involved in transmission of COVI-19 infection. This might pose an argument whether there is really a causative relationship between blood group A and the spreading of the infection? Or is it merely the effect of large percentage of blood group A in our sample? How can we confirm the transmission of the infection between family members? These questions might pose limitations of our study and make restrictions on generalizations or conclusions that might stem from this study. However, we strived to confirm the spread of infection by precisely following the clear chain of transmission, the incubation period, and appearance of symptoms among family members as related to index family member as explained in materials and methods.

To elaborate on genetic background of family members with same blood group, we found that almost 52 (51%) family members who tested positive contracted the infection from their parents. Having this in mind, and with the notion that we have an equal number of infected sons and daughters in these families (27 sons and 25 daughters), one can predict that these children inherited similar XG antigens from their parents and their might be a strong relation of the antigen to COVID-19 transmission. See the discussion above about X-chromosome and XG antigen inheritance and elaborate more on its relation to ABO blood group.

Our above findings contradicted an early study by Fan Q. et al. (referred to earlier in this study) which predicted that females to be more prone to contract COVID-19 than males. However, their study is a community-based study where genetic variations in the blood group might be greater than in same family members.

In the end, we propose an epidemiologic evidence of the direct relation of blood group for people living in the same household on the transmission of COVID-19 infection. However, we cannot supervise subjects in our study who were exposed to the infection without showing any symptoms. These subjects have never been

exposed to the virus, are resistant to the infection, or silent carriers who did not test and did not show any symptoms. They might be considered as silent transmitters of the infection. This could also be due to the firm quarantine measurements that were taken at the beginning of the pandemic where infected persons and their contacts must be quarantined and isolated from others in special COVID-19 centers or at home.

The type of blood is not associated with risk of progression to severe disease requiring intubation or causing death, nor is it associated with higher peak levels of inflammatory markers [24].

The first published genetic evidence that ABO may have a regulatory role in an inflammatory mediator, was the finding that soluble intercellular adhesion molecule 1 (sICAM-1) concentrations were associated with genetic variation at the ABO and ICAM1 loci in women. This finding could have a potential implication on a diverse array of immune-mediated disorders [25].

Unlike flu, COVID-19 symptoms such as ageusia and anosmia are not accompanied by nasal obstruction or other rhinitis-like symptoms. This might be due to direct damage of the virus to the olfactory and gustatory receptors. More work needs to be done to unravel the pathogenesis of corona virus for sensorineural olfactory loss [26].

We also elaborate on the loss of smell and taste in relation to the loss of appetite, which considered as GIT manifestations of the COVID-19 virus [27], and weight loss. Loss of smell and taste, in addition to the fact that the virus receptors found in epithelial cells of the oronasopharengeal area and in the GIT mucosa, which are considered as direct target of the virus, may have a psychological effect on a family member. Parents were unable to detect the smell of gas, toxins, burn, salt while cooking, which might cause dangerous results. On other hand, symptoms of GIT and/or loss of smell and taste can lead to loss of appetite and indirectly to weight loss. Women are more likely to experience emotional issues such as depression, anxiety related to olfaction [28]. Loss of appetite was highest in patients who lost both senses (smell and taste) compared to whom lost one of them only. Surprisingly, in our study, the highest percentage of patients did not

lose any sense. In addition to that, many patients in our study have chosen to change their lifestyle during sickness time. They attributed this to many reasons such as food was tasteless and had no smell, they felt so tired and helpless. They thought it was better to eat healthy and lead an active lifestyle in order to support their immunity and fight the disease. Depending on the herbs, walking, eating fresh vegetables and fruits were also favourable practices by our patients. The weight loss mentioned here was only related to the quarantine time (14 days).

In conclusion, our results prove the transmission of COVID-19 among same family members might follow the model for ABO transfusing compatibility. It could depend on the presence and amount of Anti-ABO antibodies (Anti-A and Anti-B antibodies) in the sera of individuals which is highly variable and constitutes the foundation for variability in acquiring the infection or neutralizing the spike protein of the SARS-CoV-2 virus [29, 30, 31, 32].

Conclusions: Blood group O was associated with most cases of COVID-19 among members of the same family who have clear transmission chain and known index family member. However, we could not prove a causative relationship between this blood group or other important blood groups such as type A, and COVID-19 spread. Here, we provide an epidemiological observation. Transmission of infection might follow the pattern of compatibility of ABO transfusion among family members. However, further laboratory work is necessary to prove this theory at the molecular level.

Ethics approval: The IRB board and the Hebron University graduate office committee approved this research and granted us the permission to start the field work. We took verbal consent from all participants to voluntarily participate in this study. We also guarantee the right to withdraw from the study at any time. We ensure the confidentiality of personal and clinical data as per the Helsinki agreement.

Conflicts of Interest: we declare that there is no conflict of interest.

Funding: we did not receive any fund for this study from any source.

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