ABO blood groups and psychiatric disorders: a Croatian study

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Background. The prevalence of ABO alleles is different in different populations, and many studies have shown a correlation between the occurrences of some diseases and different genotypes of ABO blood groups. The aim of this study was to determine whether there is a significant association between psychiatric syndromes and ABO blood groups.

Materials and methods. This case-control study involved 156 psychiatric patients and 303 healthy, unrelated, voluntary blood donors. Genomic DNA was isolated from blood on a QIAcube device using a QIAamp DNA Blood mini QIAcube kit. ABO genotyping on five basic ABO alleles was performed using allele-specific polymerase chain reaction analysis.

Results. Compared with healthy subjects, a significantly higher proportion of psychiatric patients had AB blood group (χ^2=9.359, df=3, p=0.025) and, accordingly, a significantly higher incidence of A1B genotype (χ^2=8.226, df=3, p=0.042). The odds ratio showed that psychiatric disorders occur almost three times more frequently in carriers of AB group compared to other blood groups. However, no statistically significant difference was found in the distribution of ABO blood groups among patients with different psychiatric diagnoses. Likewise, no correlations were found between ABO blood groups and other characteristics of the psychiatric patients (sex, psychiatric heredity, somatic comorbidity, suicidality).

Conclusions. The results of this study support the hypothesis of an association between psychiatric disorders and ABO blood groups. The probability is that psychiatric disorders will occur almost three times more frequently in carriers of AB group compared to other ABO blood groups in the Croatian population.

Keywords: ABO blood group, alleles, genotypes, psychiatric disorders.

Introduction

Between the end of the last century and the beginning of this one, blood groups and their significance have been increasingly investigated and written about. In addition to scientific research, popular curiosity is also increasing. Most of the research is based on phenotypic divisions of blood groups and primarily related to the ABO system. This is the most important blood group system in transfusion and transplantation medicine, as it represents an immunological barrier against incompatible blood transfusions or transplantation of incompatible organs[1]. The clinical importance of antibodies to the ABO system is due to the natural presence of such antibodies and their high reactivity, which can be the cause of haemolytic transfusion reactions, haemolytic disease of the newborn and rejection of the transplanted organ[1,2].

The prevalence of ABO alleles in different populations is not the same, and many studies have shown a correlation between the occurrence of some diseases with different genotypes of ABO blood groups. The most commonly reported correlations concern cardiovascular and gastroduodenal diseases, tumours, and infections[3-8]. Likewise, there is an established correlation between ABO blood groups and certain psychiatric disorders, although contradictory results have been published[9-22].

The relationship between psychiatric disorders and blood groups can be interpreted in relation to neurotransmitters and enzymes responsible for their metabolism. As vulnerability to psychiatric disorders can be determined by enzymes and genes, it is believed that there is a genetic link between blood groups and mental state[11,19,22,23]. Although not present in Europe, in Japan there is a widely accepted theory about the influence of blood type on personality and mental status (a certain blood group determines personality, temperament, and compatibility with others). The theory has also been adopted in neighbouring Asian countries such as South Korea and Taiwan[24-27].

Given the contradictory results of the research, there is still debate in this area. Is a certain blood type somehow connected to the occurrence of certain psychiatric disorders, i.e. do some psychiatric disorders

occur more frequently in subjects with specific blood groups? The aim of this study was to determine whether there is a significant association between psychiatric disorders and ABO blood groups.

Materials and methods

Participants

The group studied consisted of inpatients from "Sveti Ivan" Psychiatric Hospital in Zagreb, Croatia. Data were collected during 2015, from January to May. A total of 156 psychiatric patients participated in the study, with an equal number of males and females. All patients signed informed consent to participation in the study. The average age of respondents was 44.8 years (standard deviation [SD]=12.1). The youngest respondent was 19 and the oldest 71 years of age. Most of the respondents (66.9%) had completed secondary school, 22.7% had completed only elementary school, while 10.3% had higher education. With regards to marital status, 45.1% were single, 36.6% were married, 13.7% were divorced, and 4.6% were widowed. The patients' diagnoses were determined by two psychiatrists, according to the International Classification of Diseases (ICD)-10 diagnostic criteria: 38.7% of patients had a primary diagnosis of a psychotic disorder, 27.1% a primary diagnosis of addiction, 26.5% had mood disorders, and 7.7% of patients had a primary diagnosis of a personality disorder. Overall, 45.1% reported positive psychiatric heredity, 27.4% of patients had attempted suicide, 8.9% were suicidal at the time of the trial, whereas the majority (63.7%) denied suicidal ideation and intent. Almost half of the respondents (49.3%) had at least one somatic disease diagnosed, with the most frequent being hypertension (17.9%).

The second group (the control group) of healthy, unrelated, voluntary blood donors was also studied. Following approval by the Ethical Committee of the Croatian Institute for Transfusion Medicine, the study was conducted on 303 blood donors who gave consent to further testing of their blood samples. The control group consisted of 180 men and 123 women, aged between 18 and 76 years old.

Methods

Samples from all patients and blood donors in the control group were collected into Vacutainer PPT tubes (8.5 mL) (Beckton Dickinson, Franklin Lakes, NJ, USA). ABO genotyping was performed in the Department of Molecular Diagnosis of the Croatian Institute of Transfusion Medicine. The samples were centrifuged for 10 minutes at 1,215 *g* and frozen at a temperature of −80 ºC. Genomic DNA was isolated from the whole blood by QIAcube (Qiagen GmbH, Hilden, Germany) using a QIAamp DNA Blood mini QIAcube kit (Qiagen).

ABO genotyping was performed by allele-specific polymerase chain reaction (PCR) in eight parallel assays[28]. Testing was performed in 12-sample series. The PCR products obtained were subjected to gel electrophoresis and ultraviolet light with a wavelength of 254 nm and photographed by Kodak camera. Using this method of separating five basic ABO alleles, 15 ABO genotypes can be determined.

Statistical analysis

Statistical data were analysed using the SPSS statistical software, version 20.0 for Windows (SPSS Inc., Chicago, IL, USA). The results obtained are presented in the form of frequencies and percentages. A chi-square test was used to determine the significance of differences in the presence of individual blood groups within and between the two study groups (psychiatric patients and control blood donors), as well as among the subjects with different psychiatric diagnoses. A chi-square test was also used to investigate the association of blood groups and some characteristics of the psychiatric patients (sex, psychiatric heredity, suicidality, somatic comorbidity). The level of statistical significance was set at $p \leq 0.05$.

Results

Comparison of the prevalence of ABO blood groups between psychiatric patients and the control group

The distribution of individual ABO blood groups in psychiatric patients and healthy subjects (control group) is shown in Table I. It is evident that blood groups A and O were predominant in both psychiatric patients and healthy subjects. However, a comparison of the groups in psychiatric patients and healthy subjects, using the chi-square test, revealed a statistically significant difference between the two (χ^2=9.359, degree of freedom [df]=3, p=0.025). The proportion of subjects with AB blood group was significantly higher among psychiatric patients than among healthy subjects (Table II). The odds ratio (OR) indicated that psychiatric disorders occur almost three times more frequently in people with AB blood group than in people with other blood groups (Table I).

Table I - Distribution of ABO blood groups in psychiatric patients and in the control group.

ABO blood groups	Psychiatric patients n=156 (%)	Control group n=303 (%)	OR (95% CI)	p
O	50 (32.1)	122 (40.2)	0.70 (0.47-1.05)	0.0858
A	59 (37.8)	115 (38.0)	0.99 (0.67-1.48)	0.9778
B	27 (17.3)	50 (16.5)	1.06 (0.63-1.77)	0.8267
AB	20 (12.8)	16 (5.3)	2.64 (1.33-5.25)	0.0057

OR: odds ratio; 95% CI: 95% confidence interval.

Table II - Comparison of ABO phenotypes in patients and the control group.

ABO phenotype	Psychiatric patients χ^2 (p)*		Control group χ^2(p)*	
O	1.23	(0.27)	0.62	(0.43)
A	0.00	(0.98)	0.00	(0.99)
B	0.03	(0.87)	0.01	(0.90)
AB	4.93	(0.03)	2.53	(0.11)

* Standardised residuals transformed into χ2 values.

The distribution of certain genotypes in psychiatric patients and healthy subjects is shown in Table III. The most common genotypes were O1O1, O1A1, O1B and A1B in both groups. The chi-square test was used to determine whether the two groups differed in relation to the presence of particular genotypes. Given the small number of subjects with individual genotypes, only the most common genotypes were selected for analysis. The comparison of psychiatric patients and healthy subjects showed a statistically significant difference (χ^2=8.226, df=3, p=0.042). The incidence of A1B genotype was significantly higher among psychiatric patients than among healthy subjects (Table IV).

Table III - Distribution of ABO genotypes in psychiatric patients and in the control group.

ABO genotype	Psychiatric patients n (%)		Control group n (%)	
O1O1	47	(30.1)	113	(37.3)
O1O2	3	(1.9)	8	(2.6)
O2O2	0	(0.0)	1	(0.3)
A1A1	8	(5.1)	12	(4.0)
O1A1	35	(22.4)	82	(27.0)
O2A1	1	(0.6)	5	(3.6)
A1A2	3	(1.9)	5	(1.7)
O1A2	10	(6.4)	11	(3.6)
O2A2	2	(1.3)	0	(0.0)
A2A2	0	0.0	0	0.0
BB	0	(0.0)	2	(0.7)
O1B	27	(17.3)	48	(15.8)
O2B	0	0.0	0	0.0
A1B	16	(10.3)	13	(4.3)
A2B	4	(2.6)	3	(1.0)

Table IV - Comparison of psychiatric patients and control group according to genotypes O1O1, O1A1, O1B and A1B.

ABO genotype	Psychiatric patients χ^2 (p)*		Control group χ^2 (p)*	
O1O1	0.58	(0.45)	0.28	(0.60)
O1A1	0.30	(0.58)	0.14	(0.70)
O1B	0.23	(0.63)	0.12	(0.73)
A1B	4.41	(0.04)	2.16	(0.14)

* Standardised residuals transformed into χ^2 values.

The association of ABO phenotypes and genotypes with specific psychiatric diagnoses

The distribution of ABO blood groups in patients with different psychiatric diagnoses is shown in Table V. No statistically significant difference in the frequency of patients with a particular blood group in relation to diagnosis was determined, i.e. the incidence of ABO blood groups did not differ significantly between patients with different psychiatric diagnoses (χ^2=9.205, df=9, p=0.419).

Table V - Distribution of ABO blood groups in psychiatric patients according to their diagnosis.

ABO blood groups	Primary psychiatric diagnoses			
	Mood disorder n (%)	Psychotic disorder n (%)	Addiction n (%)	Personality disorder n (%)
O	12 (29.3)	18 (30.0)	14 (33.3)	5 (41.7)
A	16 (39.0)	18 (30.0)	20 (47.6)	5 (41.7)
B	7 (17.1)	14 (23.3)	6 (14.3)	0 (0.0)
AB	6 (14.6)	10 (16.7)	2 (4.8)	2 (16.7)

The chi-square test was also used to verify whether the incidences of the most common genotypes (O1O1, O1A1, O1B and A1B) differed between patients with different psychiatric diagnoses. Given the small number of subjects per category, the analysis was conducted without the group of patients with a primary diagnosis of personality disorders. No statistically significant difference was found, i.e. patients with different psychiatric diagnoses did not differ significantly with respect to the ABO genotype (χ^2=5.413, df=6, p=0.492).

The association of ABO phenotypes and genotypes with some characteristics of the psychiatric patients

The association of ABO phenotypes and genotypes with various characteristics of the psychiatric patients included in the study (gender, psychiatric heredity,

Table VI - Association between ABO blood groups and different characteristics of the psychiatric patients.

Patients' characteristics	χ^2		p	
	ABO phenotype	ABO genotype	ABO phenotype	ABO genotype
Sex	4.204	1.992	0.240	0.574
Psychiatric heredity	4.231	1.749	0.238	0.626
Somatic comorbidity	4.354	5.554	0.226	0.135
Suicidality	0.714	2.730	0.870	0.435

somatic comorbidity, suicidality) was also investigated. No statistically significant findings were obtained. The results are shown in Table VI.

Discussion

In this study, we investigated the relationship between psychiatric disorders and ABO blood groups. Among psychiatric patients, there was a significantly higher proportion of individuals with blood type AB (12.8%) compared to proportion of the control group (5.3%) (p=0.0057). Psychiatric disorders occur almost three times more frequently in subjects with AB blood type compared to subjects with other blood types (OR 2.64; 95% CI 1.33-5.25), but no statistically significant associations were found between different blood groups and particular diagnostic categories of psychiatric disorders, i.e. patients with different psychiatric diagnoses did not differ significantly by blood type.

The results of other studies on the association of ABO blood groups with psychiatric disorders are contradictory. Some studies pointed to the link between ABO blood type and personality rather than psychiatric disorders[27]. A study conducted in 1976 found an increased frequency of blood group A in patients with depressive disorders, and of blood group O in patients with schizophrenia[29]. Vasan *et al*. collaborated in a study on the relationship between ABO blood group and dementia and did not establish any difference in the risk of dementia according to blood group[21]. A study on the correlation between blood groups and opioid addiction revealed an association of gene for D_2 receptors with the addiction to psychoactive substances, and the frequency of genotype A1A1 was significantly higher among opiate addicts[19]. Since the 1950s there have been several studies describing a clear correlation between blood group A and schizophrenia, and blood group A and unipolar depression[9,10]. Studies from the 1960s and from 2002 showed significant associations between blood group O and bipolar affective disorder[10,17,29]. Likewise, blood type O was associated with involuntary melancholy and depression and, in some studies, an increased vulnerability to schizophrenia[9,12,16,30]. Other studies have shown relationships between bipolar affective disorder, unipolar depression and blood type O, and between involuntary depression and blood group A[9-12]. Rinier and colleagues pointed to a negative association between blood group A and bipolar affective disorder[12], and other authors to an association between blood group A and unipolar depression[10]. A stronger association was found between blood group O and bipolar affective disorder type I, while bipolar affective disorder type II was associated with blood groups A and B[10,12,17]. An association was found between blood group A and obsessive-compulsive disorder, while no association was found between anankastic symptoms in psychotic disorders among patients with blood type A[11].

Thus, findings on associations between psychiatric disorders and blood groups are more controversial and weaker than those in relation to the association of blood groups and somatic illnesses[23,24]. Some previous research does, however, suggest that the association between blood groups and psychiatric disorders may be determined by a developmental relationship, i.e. a genetic condition, although the results so far are still being considered[10,18,22,23,31].

The findings of our study on the association between psychiatric diseases and ABO genotypes showed that the most common genotypes in both groups (psychiatric patients and the control group) were O1O1, O1A1, O1B and A1B, which are the most common genotypes in the Croatian population. However, a statistical comparison found that there was a significantly higher frequency of A1B genotype among psychiatric patients. Nevertheless, patients with different psychiatric diagnoses did not differ significantly by ABO genotype. The limiting factor of the research in this part of the study was the relatively small numbers of patients with the different psychiatric disorders for mutual comparison.

Previous studies also pointed out a possible linkage between individual genotypes and various mental disorders. For example, a significantly increased frequency of genotype A1A1 was found in opiate addicts in a study published in 2011[19]. When comparing the representation of A and B alleles in the world, there is a much higher prevalence of the A allele (about 21%) compared to the B allele (about 16%)[1]. It would be interesting to identify clinical links or causes of association between the AB allele with psychiatric diseases. It is well known that dopaminergic and noradrenergic systems play important roles in addiction, drug abuse, impulsiveness and socially unacceptable behaviour[32,33]. Some studies indicate that subjects with O blood group have greater production of noradrenaline compared to subjects with other ABO blood groups[32]. The more frequent occurrence of bipolar affective

disorder in subjects with O blood group is, according to some studies, due to changes in the levels and activity of the dopamine beta hydroxylase enzyme involved in the conversion of dopamine neurotransmitter to noradrenaline[32,34,35]. In bipolar affective disorder the activity of dopamine beta hydroxylase is enhanced, while in depression it is reduced[32,36]. Subjects with O blood type are also more susceptible to developing schizophrenic disorders, probably due to "excessive dopamine activity"[32]. According to some studies, the activity of monoamine oxidase is lower in subjects with blood group O than in subjects with other blood groups, resulting in higher levels of dopamine in the former, which is significant because monoamine oxidase is a sign of behavioural disorders, psychiatric disorders and neurodegenerative diseases[29-32,34,35]. There is an elevated level of cortisol in the blood type A carriers, which is responsible for increased mental stress, cancer development, hypertension, heart disease and myocardial infarction[31,32,35-37]. According to some studies, high doses of cortisol play a significant role in the development of Alzheimer's dementia[32]. A high incidence of obsessive-compulsive disorders, commonly associated with elevated cortisol levels and decreased melatonin levels, was found in the group A blood donors[32,37]. Likewise, some studies found higher concentrations of noradrenaline and adrenaline in blood group A subjects compared to subjects with other blood groups; these catecholamines are correlated with stress, and responsible for the induction of anger and aggression[32,34,35,38]. It has been reported that the excretion of nitrogen oxide is faster in carriers of B and AB blood groups than in individuals with other blood groups; this neurotransmitter is considered to be responsible for the development of depression and other psychiatric disorders because it is a critical neuroinflammatory regulator[32,34,38,39].

Conclusions

The results of this study support the hypothesis of a significant association between psychiatric disorders and ABO blood groups: more specifically, there is an increased tendency for patients with AB blood group to develop psychiatric disorders. It was found that the likelihood of developing a psychiatric disorder is almost three times higher in individuals with AB blood group than in those with other blood groups in the Croatian population.

With regards to a relationship between individual ABO blood types and the different psychiatric disorders investigated, no statistical difference was found. Given the contradictory results of other studies, there is need for further research, either in larger population samples, or by narrowing down the study of the correlation between individual symptoms and the blood groups rather than whole diagnostic entities. Either way, more studies are necessary to confirm the findings and to identify the mechanism of association between blood groups and the emergence of psychiatric disorders.

Authorship contributions

SVP, TV and IJ designed the study; SVP, EI and JB-P collected and analysed data; SVP, TV and EI drafted the manuscript; JBP, IJ, TV, IF and SVP reviewed and revised the manuscript.

All Authors critically reviewed and revised the manuscript drafts, approved the final version of the manuscript and take responsibility for the integrity of the data and accuracy of the data analysis.

The Authors declare no conflict of interests.

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