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ORIGINAL RESEARCH

Sociodemographic, Clinical and Genetic Correlates of Aggressive and Auto-Aggressive Behaviour in Alcohol-Dependent Individuals – Preliminary Study

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Purpose: Reducing the risk of aggressive behaviour requires preventive measures that depend on our knowledge of predisposing factors. The study's aim was to compare sociodemographic variables, clinical variables and the frequency of gene polymorphisms predisposing to destructive behaviour between subpopulations of individuals with a history of suicidality and/or of aggression, both being treated for alcohol dependence.

Patients and Methods: Sixty-nine patients hospitalised for alcohol dependence participated in the study. The sociodemographic, clinical (SADD, BPAQ) and genetic variables were compared between subpopulations of alcohol-dependent patients selected according to type of aggressive behaviour, including a history of suicidal behaviour and control nonalcohol-dependent group. Polymorphisms of MAOA, COMT, DRD2 and DAT1 loci that are known as risk factors of mental dysfunctions were investigated.

Results: The subpopulation of patients with suicide attempts had a longer time in education than patients with aggressive and suicidal behaviour (11.9 vs 9.7 years). Patients with suicide attempts and patients with aggression had lower levels of alcohol dependence than patients with comorbid suicide attempts and concomitant aggression. For the MAOA gene lower frequency of the G/G genotype with tendency to statistical significance was observed among patients burdened by suicidal behaviour in comparison to patients with aggression and a significantly higher A/G genotype compared to cases with aggression and controls. In the case of COMT polymorphism, the G/G genotype was reported significantly less often among patients with suicide attempts and comorbid aggression than among patients with control group).

Conclusion: Compared to patients with either only suicidal tendencies or aggression, those with comorbid aggression and suicide attempts are characterised by poorer social performance. Genetic variation in MAOA loci may be a risk factor for impulsive behaviour like suicidal behaviour, and especially aggression.

Keywords: gene polymorphisms, aggression, suicide behaviour, alcohol-dependence

Introduction

Aggression is a behaviour involving threats or action that may cause pain, retreat or loss of coping capacity.[1] Aggressive behaviour is considered to be verbal or physical aggression that can be directed at inanimate and animate surrounding objects (against other persons or towards the self; ie, auto aggression in the form of self-harm or suicide attempts).[2] In addition, aggression after taking psychoactive substances is distinguished in the aggressive behaviour stratification.

Factors predisposing aggressive behaviour include environmental and biological variables like genetic conditions. The particular importance of genetic factors is emphasised in determining, among other things, temperament traits, cognitive functions and personality disorders like eg, antisocial, addictions, mood disorders, eating disorders, stress resistance and disruptive behavioural disorders.[3]

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An example of studies of the association of genes with destructive behaviour can be found in research on twins. Results showed that monozygotic twins were more likely than dizygotic twins to reveal a predisposition to suicide attempts.[4] The concordance rate of suicide attempts in pairs of monozygotic twins was 11.3% compared to 1.8% in pairs of dizygotic twins.[5]

Genetic studies have confirmed the involvement of specific polymorphic changes in determining particular emotional or behavioural responses and the influence of environmental factors on gene expression. For example, the moderating role of the family environment on the association of a polymorphism in the MAOA gene with antisocial behaviour has been demonstrated.[6] The MAOA gene determines the activity of the A-type monoamine oxidase enzyme, which causes the breakdown of dopamine as an emotion modulator in the limbic system.[6] In contrast, the COMT gene polymorphism, which determines the activity of catechol-O-methyltransferase (the enzyme that breaks down norepinephrine (NA) and dopamine (DA)), and the DRD2 polymorphism, which determines the density of dopamine D4 receptors, are related to the occurrence of impulsivity.[7] In addition, COMT gene polymorphisms have been shown to be associated with a higher risk of suicide attempts.[8] Some research-supported evidence suggests that genetic variation is related to suicidal and aggressive behaviour. Genetic studies conducted in this area have largely focused on variable-number tandem repeats (VNTRs), alleles and single nucleotide polymorphisms (SNPs).[9]

As mentioned, aggressive behaviours also include forms of auto aggression like self-harm and suicide attempts. The prevalence of the above in the general population is high and is associated with social and mental health dysfunctions.[10–12]

The aim of this study was to compare sociodemographic variables of age, time in education and clinical variables and the frequency of polymorphisms of genes predisposing to destructive behaviour between subpopulations of those with a history of suicidality and aggression who were treated for alcohol dependence.

Materials and Methods

The study was conducted between 2014 and 2016 on a sample of 69 alcohol-dependent and 100 non-alcohol-dependent control subjects. The study subjects were divided into subpopulations with a history of alcohol dependence who engaged in:

- suicidal attempts without aggressive actions (group no. 1, 27 subjects, mean age of the subjects was 35 years),
- suicidal attempts and aggressive behaviour (group no. 2, 18 subjects, mean age of the subjects was 38 years),
- aggressive actions without suicidal behaviour (group no. 3, 24 subjects, mean age of subjects 35 years),
- and a control group of non-alcohol-dependent subjects (group no. 4, 100 subjects, mean age of subjects 33 years).

A self-developed tool called the Pre-test for the verification of aggressive behaviour, including suicidal behaviour, was used to verify the occurrence of aggressive behaviour. On the basis of this questionnaire, patients were classified into given subpopulations.

The categorisation of patients into the suicidal behaviour group was related to any history of suicide attempts (the patient declared there had been suicide attempts in the past).

Patients were categorised into the group with aggression after being informed about the presence of at least one of the behaviours in the past. The patient declared - I have had acts of self-aggression (eg cutting the skin, so called “tracks”). Thus ‘I have been in fights, I have had conflicts with the law eg, I have a criminal record because of acts of aggression towards other people, there is I have a ‘blue card’ for my family or relatives - special police programme to protect victims of domestic violence, my relationship or marriage has broken down because of my aggressive behaviour, I have been put under duress (eg, in the form of a restraining belt) while in a medical facility because of my aggressive behaviour’.

The study was conducted in two psychiatric treatment centres in the Kuyavian-Pomeranian Voivodeship. In order to verify the presence of alcohol dependence in the subject, a short interview was conducted as regards diagnostic criteria of alcohol dependence according to ICD-10. Prior to the study, every qualified person received information about the study and its purpose and gave written consent to participate in the study. In addition, the study was only conducted on a sample of adults capable of providing informed consent with the exclusion of pregnant women.

The Following Questionnaires Were Used in the Study

An interview questionnaire of our own design that included a:

sociodemographic interview for information on gender, age, place of residence, education, occupation, livelihoods, income and marital status,
clinical interview, concerned a subjective assessment of the life situation, including relationships in the family and childhood and the presence of aggressive and addictive behaviour in the generational family.

Assessment of Alcohol Dependence Severity

Buss Perry Aggression Questionnaire (BPAQ) - for the measurement of aggression. The BPAQ contains 29 items and is designed to assess four dispositional components of aggression like Physical Aggression, Verbal Aggression, Anger, and Hostility.[13,14]

The Short Form Alcohol Dependence Data Questionnaire (SADD), in the Polish adaptation by Ziółkowski, was used to assess the depth of alcohol dependence. A score of 0–9 indicates mild dependence, 10–19 moderate dependence and scores of 20 or more indicate deep dependence.[15,16]

Genotyping

Biological samples were collected using DNA genetic material collection kit GA01 type (Hagmed, Poland). Total DNA was isolated from the buccal swabs by EurX's commercial GeneMATRIX Bio-Trace DNA Purification Kit according to the manufacturer's instructions.

Several genomic loci were investigated, which are listed in Table 1.

Allelic discrimination of SNP variants was performed using TaqMan® SNP Genotyping Assays and ViiA7 instrument in compliance with producer's protocol (Applied Biosystems, Foster City, LA, USA). Assay ID numbers used in real-time PCR reactions were as follows: C__25746809_50 for COMT, C___7486676_10 for DRD2 and C___8817698_20 for MAOA. All samples were genotyped in duplicate. The gene length polymorphism was determined by the end-point PCR. The reaction mixtures consisted of 1 U of GoTaq Flexi polymerase, 1x PCR buffer, 1,5mM $MgCl_2$, 0,2mM dNTP (Promega, USA) and specific oligonucleotide primers. For details see Table 2. The PCR products amplified with fluorescent primers were detected by capillary electrophoresis on ABI 3130xl sequencer using POP7 and GeneScan™ 600 LIZ™ Size Standard (Applied Biosystems). The non-fluorescent amplicons were separated in 4% agarose gel at 90V with M100-500 DNA size standard (DNA Gdańsk, Poland). For fragment detection, the ethidium bromide was applied.

Bioethic

The consent and approval of the Bioethics Committee of Nicolaus Copernicus University in Torun, Collegium Medicum in Bydgoszcz (consent no. KB 618/2013) was obtained prior to the start of the study. The study complies with the Declaration of Helsinki.

Table 1 Characteristics of the Genetic Polymorphisms in the Selected Loci

Gene Locus	Polymorphism Description
Catechol-O-methyltransferase gene (COMT)	A/G, transition substitution; rs4680, Val158Met
Dopamine receptor D2 gene (DRD2)	A/G, transition substitution; rs1800497, TaqIA
Monoamine oxidase A gene (MAOA)	A/G, transition substitution; rs1465108
	30 bp variable number tandem repeat (MAOA-uVNTR)
Dopamine transporter 1 (DAT1)	30 bp variable number tandem repeat (DAT1 intron 8 VNTR)
	40 bp variable number tandem repeat (DAT1 40bp VNTR in 3′UTR); rs28363170

Table 2 The Conditions of Genotyping Reactions of the Length Polymorphisms

Polymorphism	Primers Sequence 5′-3′	Primers Amount per rxn	Temperature Profile of PCR Reaction
MAOA-uVNTR	F: ACAGCCTGACCGTGGAGAAG R: GAACGGACGCTCCATTCGGA	10 pmoles	95°C – 5′; 40 cycles: 95°C – 1′, 67°C – 1′, 72°C – 1′; 72°C – 10′
DAT1 intron 8 VNTR	F: TGTGGTGTAGGGAACGGCCTGAG R: TTCCTGGAGGTCACGGCTCAAGG	15 pmoles	95°C – 5′; 40 cycles: 95°C – 1′, 67°C – 1′, 72°C – 1′; 72°C – 10′
DAT1 40bp VNTR in 3′UTR	F: 6FAM-GCTTGGGGAAGGAAGGG R: TGTGTGCGTGCATGTGG	15 pmoles	94°C – 10′; 30 cycles: 94°C – 1′, 67°C – 1′, 72°C – 1′; 72°C – 7′

Statistical Methods

Statistical analyses were carried out using the tests of the IBM SPSS Statistics 29 program. The Mann–Whitney *U*-test was used to assess differences in a single trait between subpopulations (the test was used to analyse two groups – according to the principle "round robin"). The chi-square test was also used to analyse the results (the test was used to compare frequency of variables). A significance level of $p \leq 0.05$ was adopted as statistically significant.

Results

Table 3 shows the age, time in education, source of livelihood, income, marital status, and family structure in subpopulations of alcohol-dependent patients with a positive history of suicidal attempts (group 1), suicidal attempts and aggression (comorbid problems, group 2), with aggression alone (group 3) and in the control group (group 4).

Alcohol-dependent people with suicidal tendencies and aggression (the three subpopulations) had lower levels of education, were more likely to be single, be out of work and have lower incomes than the control group.

Table 3 Comparison of the Number of Men and Women, Age and Sociodemographic Variables in Subpopulations of Alcohol-Dependent Patients and Controls

Variables	1	2	3	4
	Patients with Alcohol Dependence, with Suicide Attempts N=27	**Patients with Alcohol Dependence, with Suicide Attempts and Aggression N=18**	**Patients with Alcohol Dependence, with Aggression N=24**	**Control Group N=100**
Age	35.0±10.5	**38.4±11.6**	35.7±11.0	33.1±7.5
Education (years)	**11.9±2.2[a]**	**9.7±2.6[c]***	**11.4±2.4**	16.6±2.8
Men	**15(55.6%)[a]***	15(83.3%)[c]	24(100.0%)[b]	90(90.0%)
Women	**12(44.4%)**	3(16.7%)	0(0.0%)	10(10.0%)
Source of income:				
Full-time work	**5(18.5%)**	**4(22.2%)**	**7(29.2%)**	53(53.0%)
Economic activity	**2(7.4%)**	**1(5.5%)**	**1(4.2%)**	47(47.0%)
Mandate contract	**1(3.7%)**	**1(5.5%)**	**4(16.7%)**	0(0.0%)
Odd job	**8(29.6%)**	**7(38.9%)**	**7(29.2%)**	0(0.0%)
Benefit for unemployers	**1(3.7%)**	**0(0.0%)**	**0(0.0%)**	0(0.0%)
Social care	**3(11.1%)**	**2(11.1%)**	**1(4.2%)**	0(0.0%)
Family	**4(14.8%)**	**3(16.7%)**	**3(12.5%)**	0(0.0%)
Other	**3(11.1%)**	**0(0.0%)**	**1(4.2%)**	0(0.0%)

(*Continued*)

Table 3 (Continued).

Variables	1	2	3	4
	Patients with Alcohol Dependence, with Suicide Attempts N=27	**Patients with Alcohol Dependence, with Suicide Attempts and Aggression N=18**	**Patients with Alcohol Dependence, with Aggression N=24**	**Control Group N=100**
Profit a month:				
No income	**3(11.1%)**	**5(27.8%)**	**1(4.2%)**	1(1.0%)
Less than social-minimum	**2(7.4%)**	**2(11.1%)**	**3(12.5%)**	0(0.0%)
Social-minimum	**7(25.9%)**	**4(22.2%)**	**9(37.5%)**	2(2.0%)
Less than median average salary	**6(22.2%)**	**3(16.7%)**	**5(20.8%)**	30(30.0%)
Median average salary	**6(22.2%)**	**2(11.1%)**	**4(16.7%)**	48(48.0%)
Over median average salary	**2(7.4%)**	**2(11.1%)**	**2(8.3%)**	19(19.0%)
Other	**1(3.7%)**	**0(0.0%)**	**0(0.0%)**	0(0.0%)
Marital status:				
Single	**18(66.7%)**	**6(33.4%)**	**14(58.3%)**	27(27.0%)
Married	**3(11.1%)**	**4(22.2%)**	**3(12.5%)**	58(58.0%)
In separation	**0(0.0%)**	**0(0.0%)**	**0(0.0%)**	2(2.0%)
Concubinage	**3(11.1%)**	**2(11.1%)**	**3(12.5%)**	8(8.0%)
Divorce	**3(11.1%)**	**6(33.3%)**	**4(16.7%)**	4(4.0%)
Widower	**0(0.0%)**	**0(0.0%)**	**0(0.0%)**	1(1.0%)
Family structure:				
Full family	21(77.8%)	**12(66.7%)**	20(83.3%)	89(89.0%)
Family without father	5(18.5%)	**4(22.2%)**	3(12.5%)	8(8.0%)
Family without mother	0(0.0%)	**0(0.0%)**	0(0.0%)	2(2.0%)
Raising children by grandparents	0(0.0%)	**2(11.1%)**	0(0.0%)	0(0.0%)
Foster family	1(3.7%)	**0(0.0%)**	1(4.2%)	0(0.0%)
Child care home	0(0.0%)	**0(0.0%)**	0(0.0%)	1(1.0%)

Notes: Mann–Whitney *U*-test (for age and education data) and Chi^2 test, where statistical significance is $p<0.05$; Data shown in bold indicate the difference from the control group; Differences between a subpopulations of patients: [a]Patients with suicide attempts vs patients with suicide attempts and aggression; [b]Patients with suicide attempts vs patients with aggression; [c]Patients with suicide attempts and aggression vs patients with aggression. *trend towards a statistical significance $p<0.1$.

Those with aggression and suicide attempts (group no. 2) were older than the control group (38 vs 33 years) and the other subgroups did not differ from the control group. Those with aggression and suicide attempts (group no. 2) were more likely to come from single-parent families than the control group and the other subgroups did not differ from the control group.

The subpopulation of patients with suicide attempts (group no. 1) had a longer time in education than patients with aggressive (group no. 3) and suicidal behaviour (group no. 2) (11.9 vs 9.7 years). Patients with aggressive behaviour (group no. 3) also had a longer education time than patients with aggression and suicidal behavior (group no. 2), but the difference was not statistically significant (11.4 vs 9.7 years). The subpopulation of patients with aggression and suicidal behaviour (group no. 2) had a higher number of women than the subpopulation with aggression without suicidal behaviour (group no. 3) (almost 17% vs 0.0%).

The data of Table 4 showed that people with aggression (group no. 3) compared to controls were more likely to have aggression at home, more likely to have addiction in their family and more likely to have a family history of mental disorders.

Patients with suicide attempts and comorbid aggression (group no. 2) had higher levels of aggression (higher score of BPAQ) than patients with suicide attempts (group no. 1) and patients with only aggression (group no. 2), (113 vs 94 and 102 scores, respectively). All subpopulations of patients were higher level of BPAQ score than the control group (who had average 65 points BPAQ).

Table 4 Comparison of Selected Clinical Variables in Subpopulations of Alcohol-Dependent Patients and Controls

Variables	1	2	3	4
	Patients with Alcohol Dependence, with Suicide Attempts N=27	**Patients with Alcohol Dependence, with Suicide Attempts, and Aggression N=18**	**Patients with Alcohol Dependence, with Aggression N=24**	**Control Group N=100**
BPAQ (score)	**94.4±19.1[a]**	**113.1±21.2[c]***	**102.0±22.2**	65.9±15.2
SADD (score)	**20.3±13.0[a]***	**27.5±10.6[c]**	**23.1±8.5**	0.0±0.0
Aggression at family home (as an early life traumas)				
No	**9(33.3%)**	**8(44.4%)**	**13(54.2%)**	90(90.0%)
Yes	**18(66.7%)**	**9(50.0%)**	**11(45.8%)**	9(9.0%)
Others	**0(0.0%)**	**1(5.6%)**	**0(0.0%)**	1(1.0%)
Mental diseases in family				
No	**18(66.7%)[a]***	**16(88.9%)**	**18(75.0%)**	98(98.0%)
Yes	**9(33.3%)**	**2(11.1%)**	**6(25.0%)**	2(2.0%)
Addiction in family (nicotine, alcohol, drugs and medicaments)				
No	**7(25.9%)**	**7(38.9%)**	**8(33.3%)**	67(67.0%)
Yes	**20(74.1%)**	**11(61.1%)**	**16(66.7%)**	33(33.0%)

Notes: Mann Whitney *U*-test (for BPAQ and SADD); and Chi^2 test, where statistical significance is $p<0.05$; **Data shown in bold indicate the difference from the control group**; Differences between a subpopulations of patients: [a]Patients with suicide attempts vs patients with suicide attempts and aggression; [c]Patients with suicide attempts and aggression vs patients with aggression. *trend towards a statistical significance $p<0.1$.

Patients with suicide attempts (group no. 1) and patients with aggression (group no. 3) had lower levels of alcohol dependence than patients with suicide attempts and concomitant aggression (group no. 2) (20 and 23 vs 27 score of SADD, respectively). It should be noted that the difference in SADD score between the subpopulations of patients with suicidal behaviour (group no. 1) and patients with aggression (group no. 3) was not statistically significant.

Table 5 shows the prevalence of selected gene polymorphisms in subpopulations of alcohol-dependent patients with a positive history of suicidal attempts (group 1), suicidal attempts and aggression (comorbid problems, group 2), with aggression (group 3) and in the control group (group 4).

Among the tested loci, only in the case of the MAOA and COMT SNP-polymorphisms some differences between the particular alcohol-dependent subpopulations were observed. In detail, for the MAOA rs rs1465108 the subpopulation of patients with suicide attempts (group no. 1) had a significantly higher frequency of heterozygous A/G genotype (18.5% vs 0.0%) and tended to be significant a lower frequency homozygous G/G genotype (51.9% vs 79.2%) than the population of alcohol-dependent patients with aggression (group no. 3). This trend also persists when samples were divided into groups with the G/G variant and with variant containing at least one A allele (A/G and A/A). Comparing each patient subpopulation with the control group, the statistically significant difference in the MAOA rs1465108 genotype frequency distribution was noted once: a higher frequency of the A/G genotype (18.5% vs 4.0%) in group 1 than in controls.

In case of COMT rs4680 the alcohol-dependent participants with suicide attempts and aggression (group no. 2) had a higher frequency of the A/G genotype (66.7% vs 43.4%; the outcome has no statistical significance) and a lower frequency of the G/G genotype (5.5% vs 29.3%; trend towards statistical significance) than the control group.

The frequencies of particular variants for DAT1 intron 8 VNTR, DAT1 40bp VNTR in 3'UTR, DRD2 rs1800497 and MAOA uVNTR polymorphisms did not differ significantly between the studied groups.

Table 5 Comparison of the Polymorphisms Frequencies Between Three Patients Subpopulations and the Control Group

Variables	1	2	3	4
	Patients with Alcohol Dependence, with Suicide Attempts N=27	**Patients with Alcohol Dependence, with Suicide Attempts and Aggression N=18**	**Patients with Alcohol Dependence, with Aggression N=24**	**Control Group N=100**
MAO-A rs1465108				
G/G	14(51.9%)[b]*	13(72.2%)	19(79.2%)	65(65.0%)
A/G	**5(18.5%)[b]**	1(5.6%)	0(0.0%)	4(4.0%)
A/A	8(29.6%)	4(22.2%)	5(20.8%)	31(31.0%)
MAO-A rs1465108				
G/G	14(51.9%)[b]*	13(72.2%)	19(79.2%)	65(65.0%)
A/G and A/A	13(48.1%)[b]*	5(27.8%)	5(20.8%)	35(35.0%)
MAO-A uVNTR				
4/4	10(37.0%)	12(66.7%)	13(54.2%)	60(60.0%)
3/5	3(11.2%)	1(5.5%)	1(4.2%)	4(4.0%)
3/3	12(44.4%)	5(27.8%)	10(41.6%)	34(34.0%)
4/5	1(3.7%)	0(0.0%)	0(0.0%)	1(1.0%)
5/5	1(3.7%)	0(0.0%)	0(0.0%)	1(1.0%)
DRD2 rs1800497 (TaqIA)				
G/G	16(59.3%)	14(77.8%)	19(79.2%)	66(66.0%)
A/G	11(40.7%)	3(16.7%)	5(20.8%)	29(29.0%)
A/A	0(0.0%)	1(5.5%)	0(0.0%)	4(4.0%)
COMT rs4680 (Val158Met)				
A/A	6(22.3%)	5(27.8%)	8(33.3%)	27(27.3%)
A/G	12(44.4%)	12(66.7%)	11(45.8%)	43(43.4%)
G/G	9(33.3%)[a]	**1(5.5%)***	5(20.8%)	29(29.3%)
		-	-	1(1.0%)
DAT1 intron 8 VNTR				
6/6	20(74.0%)	11(61.1%)	16(66.7%)	62(62.0%)
5/12	1(3.7%)	0(0.0%)	-	0(0.0%)
5/6	6(22.3%)	6(33.3%)	8(33.3%)	29(29.0%)
5/5	0(0.0%)	1(5.5%)	0(0.0%)	7(7.0%)
6/12	-	-	-	-
5/13	0(0.0%)	0(0.0%)	0(0.0%)	1(1.0%)
4/6	0(0.0%)	0(0.0%)	0(0.0%)	1(1.0%)
DAT1 40bp VNTR in 3'UTR				
10/10	17(63.0%)	7(38.9%)	15(62.5%)	57(57.6%)
9/10	9(33.3%)	9(50.0%)	7(29.2%)	33(33.3%)
9/9	1(3.7%)	1(5.5%)	2(8.3%)	9(9.1%)
8/10	-	-	-	-
Lack of data	-	1(5.5%)	-	1(1.0%)

Notes: Chi^2 test (and Fisher test or with Yates correction), where statistical significance is $p<0.05$; **Data shown in bold indicate the difference from the control group**; Differences between a subpopulations of patients: [a]Patients with suicide attempts vs patients with suicide attempts and aggression; [b]Patients with suicide attempts vs patients with aggression; *trend towards a statistical significance $p<0.1$.

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Discussion

We found few differences between sociodemographic, clinical and genetic variables between the different patient subpopulations separated according to aggressive and suicidal behaviour. Patients with suicidal behaviour and aggression (comorbid problems, group no. 2) had significantly shorter education time than patients with only a history of suicidality (group no. 1). On the other hand, patients with a history of suicidality and aggression (comorbid problems) were significantly more profoundly dependent on alcohol than patients with only a history of aggression (group no. 3).

It is considered that those with an alcohol-use disorder first go to hospital for medical help at 30–40 years of age ie, after 10–12 years of drinking, when they are moderately or heavily dependent on alcohol. The same research highlights that alcohol dependence correlates with lower levels of education and lower levels of employment. In addition, a large percentage of alcohol-dependent people have marital problems. Partnership problems often involve violent behaviour, which leads to legal conflicts.[17] According to researchers, a family history of alcohol dependence but also a family history of psychiatric disorders increases the risk of alcohol dependence in children as future adults.[17]

A negative family environment promotes the risk of developing disinhibited behaviour, resulting in psychiatric disorders, including psychoactive substance use.[18] In addition, consistency in family relationships (appropriate emotional relationship and communication within the family) reduces the risk of negative behaviours such as psychoactive substance use and aggression.[19,20] Predisposition to aggressive and self-destructive behaviour should be considered in both genetic and environmental contexts due to the interplay of these factors in buffering or exacerbating negative behaviour.[21] Studies in a sample of US and European-origin individuals have demonstrated a multigene family predisposition to aggressive behaviour and the particular impact of family relationship cohesion on these behaviours, particularly in children in early adolescence.[20]

In terms of the genetic variables analysed, we found a significant difference in the A/G genotype distribution of SNP-polymorphism of the MAOA gene between patients with suicidal behaviour and patients with comorbid aggression as well as control groups. Furthermore, a frequency of the homozygous G/G genotype of the MAOA polymorphism in patients with suicidal behaviour (group no. 1) (51.9% vs 79.2%) tended to be lower than in those with aggression (group no. 3). The MAO-A gene lies on the X chromosome therefore the heterozygous A/G genotype can only occur in females. These results may be at least partly due to the different numbers of men and women in the study groups. Therefore, analysis to detect possible associations of MAOA gene variants with suicide/aggression was conducted by pooling samples containing at least one A allele on the pattern of investigating the association of the minority A allele with aggression like elsewhere.[22] The present study showed that the A/G and A/A genotype occurred at a frequency of more than 48% in patients with suicide attempts, almost 28% in patients with aggression and suicide attempts, almost 21% in patients with aggression without suicide attempts and 35% in healthy subjects (control group). The frequency of the A allele in the European population, according to the DBSNP database, was close to 30%.[23]

It is worth mentioning that the analysis in G/G vs A/G and A/A configuration showed that the difference in the G/G genotype and the A/G and A/A genotype frequencies between alcohol-dependent groups no 1 and 3 (51.9% vs 79.2% and 48.1% vs 20.8%) trended towards a statistical significance. This may suggest that the MAOA rs1465108 polymorphism could be a risk factor for impulsive behavior like suicidal behavior, especially aggression, but comorbid with alcohol drinking or side-effects of alcohol abstinence syndrome.

The link between a variant of the MAOA gene that determines lower MAOA activity, thus increased serotonin levels and aggression probably lies in the increase in impulsivity that is specific to negative affect.[22] In other words, poorly functioning MAO-A genotypes determine reduced levels of monoamine oxidase A, resulting in higher, dysregulated levels of serotonin. Certain neuronal regions that regulate affective responses to social stimuli may be sensitive to elevated serotonin levels, resulting in a deregulated and labile response.[24]

Individuals with a mutation of this gene show higher levels of aggression,[25–27] whereas people with an allelic variant conditioning higher expression show greater prosociality.[26] This antisocial tendency of poorly functioning MAO-A genotypes is exacerbated among people with adverse experiences of abuse in early life.[28,29]

No significant associations between suicidal/aggression behavior and MAOA uVNTR genotypes were discovered in the present work. It is known from other studies that higher activity of the VNTR variant has been shown to be associated

with higher enzyme expression and increased prefrontal cortex brain activity.[30] Approximately one third of men living in Western European countries have the 3R form of the gene.[31]

The studies on the COMT gene polymorphism have indicated that the homozygous variant of the G/G polymorphism (Val158Met) is associated with greater COMT enzyme activity (the enzyme contains, in this case, valine instead of methionine), which transpires as a faster breakdown of dopamine and correlates with a greater risk of developing dependence, more intensive drinking and susceptibility to aggressive behaviour.[32,33] The present study confirms that alcohol-dependent patients with suicidal behaviour and aggression (group no. 2) had shorter education time (poorer cognitive abilities) and were the most severely alcohol dependent according to SADD (score 27) (even though they had a low percentage of COMT homozygote GG). In the authors opinion, this poor education, probably was associated with harsh alcohol drinking in this subpopulation of patients due to the positive effects reward of less active COMT (in this subpopulation, the homozygote A/A was 27.8% and heterozygote A/G 66.7%).

Previous studies report an association of the Met/Met variant (homozygous A/A genotype) with lower COMT activity and thus higher dopamine concentrations, which correlates with better performance on cognitive tests.[32] Lower dopamine concentrations in the central nervous system are associated with depressed, dysphoric mood and lower motivation to act, which results in a tendency towards aggression and auto aggression, leading to unconstructive self-regulation of mood through alcohol intake.[34,35] In our study, no significant associations between COMT rs4680 polymorphism and suicidal/aggression state were reported. However, the homozygous G/G genotype frequency was lower among alcohol-dependent patients with suicide attempts and aggression than the control group, and the statistics values tended to be significant. These findings require further research to be elucidated since others showed that genotype A/A (Met/Met) prevailed in controls (29.4% vs 17%) and protected against suicidal behavior.[36]

In the current work, we also examined DAT1 intron 8 VNTR, DAT1 40bp VNTR in 3'UTR and DRD2 rs1800497 (TaqIA) polymorphisms but found no associations for any of the studied groups. The lack of differences in the distribution of DRD2 TaqIA variants between groups with and without suicidal behaviour was reported in another study.[36] However, the same research team found an association between 40 bp VNTR-polymorphism of the DAT1 gene and suicidal behavior.[36] We did not find any research on a possible influence of DAT1 intron 8 VNTR on the susceptibility to the suicidal tendencies.

Limitations of the Study

The authors recognise that the study's limitations. The main limitation is the small sample size of the different alcohol-dependent patients' subpopulations studied. We realise that analysis of genetic variables in small subpopulations may have shown random associations; these are preliminary and to reduce this risk we used the Mann–Whitney *U*-test. An additional limitation was the lack of inclusion of subpopulations of alcohol-dependent patients without aggression or suicidal behaviour. Another study limitation is the analysis of single polymorphisms instead of a broader genetic study. The study limitations are primarily due to financial constraints.

Conclusion

1. Demographics indicate that

a. Compared to healthy people, those with aggression are characterised by poorer social functioning, education and employment, lower income and a higher likelihood of being single.
b. Persons with aggression and suicide attempts were older than control subjects and were more likely to be from single-parent families.
c. Alcohol-dependent people with suicide attempts had a longer time in education than the alcohol-dependent with aggressive and suicidal behaviour.

2. Interview data indicates that

a. Individuals with aggression were at least 5 times more likely to have encountered aggression in the family home and have relatives with mental disorders than those in the control group.
b. Persons with aggression were at least twice as likelier than those in the control group to have relatives addicted to psychoactive substances (mainly alcohol).
c. Alcohol-dependent patients with aggression have lower levels of alcohol dependence than addicted patients with suicide attempts and concomitant aggression.

3. Genetic data indicates that

a. The MAOA rs1465108 polymorphisms might be considered as risk factors for suicide attempts, and especially an aggression in the comorbid with alcohol dependence. No correlation between COMT and suicidal and aggressive behaviour was found. Further studies on larger samples, considering more variables and homogeneous in terms of diagnoses, are required to verify if these polymorphic loci are risk factors only for aggression or suicidal behavior or if they increase the risk of suicide due to their impact on the predisposition to alcohol dependence or mental disorders.[37]

Practical Implications of the Research

The way to reduce aggressive behaviour is to implement addiction prevention and maintain the quality and accessibility of education so that there are no children neglected in terms of education, but also in terms of upbringing and care. On the other hand, bearing in mind the correlating factors for aggressive and self-aggressive behaviour, it is necessary to prepare and apply a socio-demographic categorisation of risk factors for aggression and self-aggression to prevent it. On the other hand, having knowledge of the biological risk factors for aggression justifies the introduction of the above-mentioned targeted measures for a given population.[38,39]

Finally, it is worth mentioning that the study population of addicted patients may have a higher risk of adverse health effects from the external environment. This is related to the socioeconomic degradation associated with addiction and extreme exposure to climate change and is particularly true for men who, in the context of environmental change and exposure, may experience stress, existential problems and suicide.[38,39]

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work. All authors have read and agreed to the published version of the manuscript.

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Disclosure

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