

5-HTTLPR Polymorphism and suicidal attempt in depressed adolescents

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Original article

SUMMARY

The World Health Organization reports that suicide is the third leading cause of death for 15-24 year-old youths and the sixth leading cause of death for 5-14 year-old children.

Mood disorders, particularly depression, are responsible for most completed suicides. This increased risk of suicide has been found in adults and adolescents.

There is increasing evidence for the hypothesis that suicidal behavior has a strong genetic contribution. Several studies have reported a positive association between the "SS" genotype and the "S" allele of 5-HTTLPR polymorphism of the serotonin transporter gene and suicidal behaviors.

Objective

The objective of this study was to establish the association of polymorphic variants of the serotonin transporter gene in depressed adolescent patients both with and without a history of suicide attempts, as well as to determine if the presence of the "SS" genotype was associated with specific characteristics of depression.

Method

The sample consisted of 53 adolescents diagnosed with depression. The diagnosis was made through the K-SADS-PL semi-structured diagnostic interview. For genomic DNA extraction a sample of blood from each patient was obtained.

Results

The genetic analysis of the genotype and allele frequencies showed no statistically significant differences between groups. However, patients with "SS" genotype had higher frequency of hopelessness. A greater number of suicide attempts were also found in patients with this genotype.

Conclusions

No differences in allele frequencies between patients, with and without suicide attempts, were observed. Nevertheless, the "SS" genotype was associated with some features of depression.

Key words: Adolescents, suicide, depression, genetics.

RESUMEN

La Organización Mundial de la Salud reporta que el suicidio es la tercera causa de muerte más frecuente para jóvenes de 15 a 24 años de edad y la sexta causa de muerte para niños de cinco a 14 años de edad.

Los trastornos del estado de ánimo, particularmente la depresión, son los responsables de la mayor parte de los suicidios consumados. Este mayor riesgo de suicidio se ha encontrado en adultos y adolescentes.

Existe cada vez mayor evidencia respecto de la hipótesis de que la conducta suicida tiene una fuerte contribución genética. Varios estudios han reportado una asociación positiva entre el genotipo "SS" y el alelo "S" del polimorfismo 5-HTTLPR del gen del transportador de serotonina y la conducta suicida.

Objetivo

El objetivo del presente trabajo fue establecer la asociación de las variantes polimórficas del gen del transportador de serotonina en pacientes adolescentes deprimidos con y sin antecedente de intento suicida y determinar si la presencia del genotipo "SS" estaba asociada a características específicas de la depresión.

Método

La muestra estuvo conformada por 53 adolescentes con diagnóstico de depresión. El diagnóstico se realizó con la entrevista diagnóstica semi-estructurada K-SADS-PL. Para la extracción del ADN genómico se obtuvo una muestra de sangre de cada uno de los pacientes.

Resultados

El análisis genético de las frecuencias de genotipos y alelos no mostró diferencias estadísticamente significativas entre los grupos. Sin embargo, aquellos pacientes con el genotipo "SS" tenían mayor frecuencia de desesperanza. En los pacientes con este genotipo también se encontró mayor número de intentos suicidas.

Conclusiones

No se observaron diferencias en la frecuencia de alelos entre pacientes con y sin intento suicida; sin embargo, el genotipo "SS" se asoció a algunas características de la depresión.

Palabras clave: Adolescentes, suicidio, depresión, genética.

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INTRODUCTION

Although suicide accounts for nearly 2% of deaths worldwide, attempted suicide is more frequent during the course of life with a prevalence of around 3.5%, estimating that from this percentage up to 10% will end in completed suicide over a 10-year period.¹ According to estimates made by the World Health Organization, by 2020 approximately one million and a half people will die from suicide and from 15 to 30 million will commit a suicide attempt.² The same organization states that currently suicide is among the five leading causes of death between 15 and 19 years of age and is the sixth leading cause of death for those of 5 to 14 years of age.³

SUICIDE IN ADOLESCENTS

Several reports suggest that suicide in young people is increasing in many geographic areas.^{4,5} For example, it has been reported that in the United States approximately 8 to 10% of adolescents have had, at some point in their life, a suicide attempt.⁶

Regarding Mexico, in 2007, 4 388 suicide deaths were reported across the country with a suicide mortality rate of 4.12 per hundred thousand inhabitants, which represents an increase of 275% compared to the suicide rate reported in 1970. What draws even more attention of this fact is that this increase is particularly marked among young people.⁷

In 2010, a cross-sectional study in 12 424 adolescents from high school public schools from the 32 states of Mexico, reported that 47% of the surveyed students had had suicidal ideation at some point in their life. In addition, 9% of students reported a history of at least one suicide attempt.⁸

PSYCHOPATHOLOGY AND SUICIDE

Suicide is often associated with many psychiatric disorders, such as mood disorders, substance abuse, and some personality disorders. In people with these conditions, the risk of suicide is 10 to 20 times higher than in the general population.²

Several researchers have suggested that mood disorders, particularly depression, are responsible for the majority of suicides in both adults and adolescents.^{9,10} In the latter group more than half will eventually made a suicide attempt, and about 10% will commit a completed suicide within 15 years after diagnosis.^{11,12}

GENETICS AND SUICIDE

In recent years there have been numerous efforts to establish the genetic basis of suicidal behavior. According to Bondy et al., it is estimated that 43% of the variability in suicidal be-

havior could be explained by genetics, while the remaining 57% is due to environmental factors.¹

Several molecular studies have focused on finding associations for the genes of enzymes, transporters and proteins of the serotonin receptor [5-hydroxytryptamine (5-HT)] required for synaptic neurotransmission.¹³ In this regard, there is evidence that the serotonin transporter (SLC6A4) gene is associated with suicidal behavior.¹⁴ This is a key protein involved in the regulation of the serotonergic neurotransmission while being responsible for the synaptic serotonin uptake and for the site of action of several antidepressants. This gene is located on the long arm of chromosome 17 (17q11.1-12); in said gene there is a polymorphism identified in the promoter region called 5-HTTLPR, which consists in the insertion/deletion of 44 base pairs, resulting in two alleles, a short form or "S" (deletion) and the long variant or "L" (insertion). Several studies have found a positive association between the 5-HTTLPR polymorphism "SS" genotype and "S" allele and completed suicide, suicide attempts and a family history of suicidal behavior.^{15,16}

With regard to adolescents, some studies have analyzed the 5-HTTLPR polymorphism and its relationship to suicidal behavior, obtaining different results. In a study conducted by Zalsman et al. in 48 patients aged 16 to 24 years assessed by K-SADS-PL and SCID instruments, there was no significant association between 5-HTTLPR polymorphism and suicidal behavior found. However, there was a significant association between the presence of violent behavior in suicidal adolescents and the LL genotype of the serotonin transporter.¹⁷ In another recent study conducted by the same author in 60 adolescents, also assessed with the K-SADS-PL (32 with suicide attempt and 28 without it), no significant differences were found when analyzing this same polymorphism.¹⁸

In our country the number of suicides in children and adolescents has increased considerably in the last decade. Nonetheless, there is relatively little research aimed to study such phenomenon. The objective of this study was to establish the association of polymorphic variants of the serotonin transporter gene in depressed adolescent patients both with and without a history of suicide attempts, as well as to determine if the presence of the "SS" genotype was associated with specific characteristics of depression.

METHODS AND MATERIALS

The recruitment of patients was performed consecutively during the period between August and December, 2010 regarding outpatient, hospitalization and emergency services of the "Dr Juan N. Navarro" Children's Psychiatric Hospital. All patients from 12 to 17 years of age diagnosed with depression with and without a history of suicide attempt, regardless of comorbidity or received treatment were included. Acceptance to participate in the study was per-

formed by means of written informed consent by the patient and parent or guardian.

The semi-structured diagnostic interview *Schedule for affective disorders and schizophrenia for school-aged children-present and lifetime version* (K-SADS-PL) – in its validated Spanish version – was conducted to all patients.¹⁹

The K-SADS-PL was adapted from the K-SADS-P, which was developed by William Chambers and Joaquin Puig-Antich. This interview was designed to assess current and past episodes of psychopathology in children and adolescents according to the DSM-III-R and DSM-IV criteria.

After completing the interview, a blood sample for the collection and analysis of genotypes and alleles was taken through the polymerase chain reaction, using the conditions described by Camarena et al.²⁰

For the description of clinical and demographic characteristics frequencies were used; and percentages for categorical variables; and means and standard deviation (SD) for continuous variables. As hypothesis testing in patients' comparison a Chi Square (χ^2) was used for categorical contrasts, and unadjusted risks were calculated. Also, the Student's t test was used to compare means. The statistical significance level was fixed with a $p \leq 0.05$.

RESULTS

53 patients were included of which 54.7% were females ($n=29$). The average age was 14.25 ± 1.7 years of age (12-17 year interval).

22.6% ($n=12$) had depression as a single diagnosis, 26.4% ($n=14$) had a comorbid disorder, 34% ($n=18$) had two,

11.3% ($n=6$) had three and, finally, 5.7% ($n=3$) had four comorbid disorders. Table 1 shows the distribution of major comorbid diagnoses of patients with and without a history of suicide attempts and the total percentage of the sample.

Of the total sample, 26.4% ($n=14$) had at least a clear suicide attempt according to K-SADS-PL (score of 3, both in the severity and lethality). Figure 1 shows the main methods used in the last suicide attempt reported by patients.

We found some significant differences in the frequency of some symptoms of K-SADS-PL depression supplement between suicidal and non-suicidal patients. In particular, in the first group there was a greater frequency of decreased appetite (57.1% vs. 28.2%, $\chi^2=7.3$, $gl=2$, $p=0.025$), weight loss (21.4% vs. 12.8%, $\chi^2=10.24$, $gl=2$, $p=0.006$) and sensitivity to rejection (71.4% vs. 41%, $\chi^2=6.82$, $gl=2$, $p=0.03$).

The analysis of the genotype and allele frequencies showed no significant differences between groups (Table 2). However, patients with "SS" genotype had higher frequency of hopelessness (66.7% vs. 31.4%, $\chi^2=6$, $1 gl$, $p=0.014$), (RM=4.36, IC 95% 1.29-14.66). A greater number of suicide attempts was also found in patients with this genotype (1.33 ± 1.23 vs. 0.66 ± 0.68 , $t=2.57$, $51 gl$, $p=.013$).

DISCUSSION

The international medical literature has reported that 40 to 70% of adolescents with depression have two or more comorbid diagnoses, the most frequent dysthymia, anxiety disorders, attention deficit hyperactivity disorder, conduct disruptive disorders and substance abuse.²¹ The results of

Table 1. Comorbidity of depressed patients

Comorbid diagnosis	Patient with S.A.	Patient without S.A.	Total percentage
Dysthymia	0	1	1.8
Generalized anxiety disorder	3	9	22.6
Panic disorder	0	1	1.8
Agoraphobia	0	1	1.8
Separation anxiety	0	6	11.3
Simple phobia	0	3	5.6
Social phobia	1	8	16.9
Attention deficit hyperactivity disorder	6	11	32.1
Oppositional defiant disorder	4	12	30.2
Dissocial personality disorder	0	1	1.8
Alcohol	2	0	3.7
Cannabis	0	1	1.8
Inhalants	0	1	1.8
Bulimia	1	2	5.6
Enuresis	0	1	1.8
Encopresis	0	1	1.8
Posttraumatic stress disorder	3	1	7.5

S.A.= Suicide attempt.

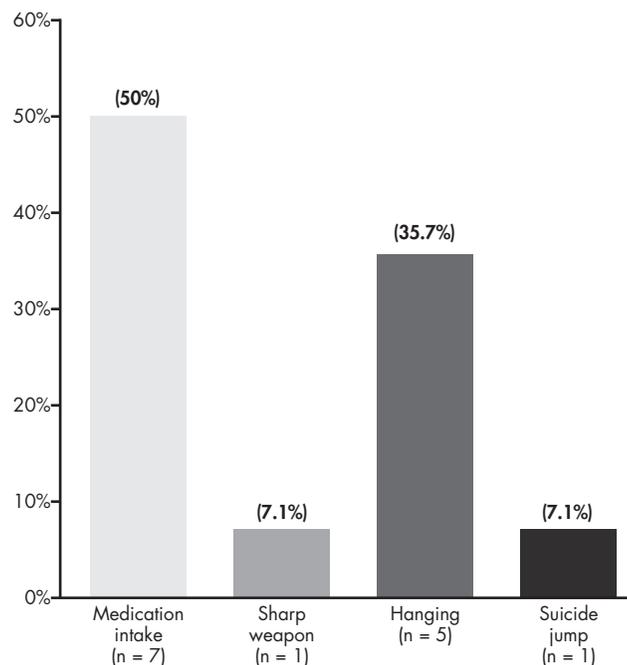


Figure 1. Method used in the suicide attempt.

Table 2. Frequency of 5-HTTLPR polymorphism genotypes and alleles of SLC6A4 gene

Depression	Genotypes			Alleles	
	SS	SL	LL	S	L
With suicide attempt	5 (0.36)	7 (0.50)	2 (0.14)	17 (0.61)	11 (0.39)
Without suicide attempt	13 (0.33)	18 (0.46)	8 (0.21)	44 (0.56)	34 (0.44)

Genotypes: $\chi^2=0.26$, $gl=2$, $p=0.87$

Alleles: $\chi^2=0.15$, $gl=1$, $p=0.69$

our study are no exception as 77.4% of the sample had one or more comorbid disorders, where attention deficit hyperactivity disorder, oppositional defiant disorder and generalized anxiety disorder are the three main disorders.

In the suicide group, a special mention deserves the presence of posttraumatic stress disorder (PTSD), as in our study, three of the four cases diagnosed reported having made a suicide attempt. Research in this area report that people who have a diagnosis of PTSD are 2.7 times more likely to have a suicide attempt compared with the rest of the population.²²

In this study the appetite and weight loss clinical variables, as well as rejection sensitivity, were the symptoms most frequently associated with the presence of suicide attempts. While the significant reduction in appetite and the subsequent weight loss are clinical features constantly reported by patients diagnosed with depression, as far as we are aware there are no studies that report the association of these two clinical features with the presence of a suicide attempt. However, considering that both features are part of the diagnosis of atypical depression, their presence in suicidal adolescents could be part of a different subtype of depression in this age group. Regarding the presence of increased sensitivity to rejection, too little is known about its relationship to suicidal behavior. This is why more studies on our environment must be carried out in order to assess which are the clinical features of depression in adolescents who attempt suicide, compared to those who do not try.

In connection with the suicide methods used, there were also no differences with studies examining this variable. As a general rule, the most violent and lethal methods such as hanging are used in completed suicides, while non-violent methods such as drug intake are often preferred in suicide attempts.^{23,24} In our sample medication intake was the most used method in 50% of cases.

In our study we found no association between the 5-HTTLPR polymorphism variants and the history of suicide attempt, which echoes the findings of no association in children and adolescents.^{25,26} However, we found an association of an increased number of suicide attempts in subjects with "SS" genotype. This could be explained, in part, because the presence of this genotype has been associated with higher levels of impulsivity and aggression.²⁷

As for the comparison of this study with other studies conducted in adolescent clinical population, our findings are similar to no association results recently reported, where similar genotype frequencies were found.¹⁸ The phenotype of suicide attempt is highly heterogeneous, therefore, to examine features associated with such behavior allows more homogeneous features that help finding susceptibility genes for the development of complex behaviors such as suicide – as evidenced by the meta-analysis of Clayden – which reports that there is no correlation between genetic polymorphisms and suicidal behavior in general. Nevertheless, it finds a significant association between subgroups of people with suicide attempt and the 5-HTTLPR serotonin transporter gene.¹⁶

Moreover, analysis of the clinical characteristics showed an interesting finding in patients with "SS" genotype, which had a higher severity of hopelessness. This supports the data showing that patients with this symptom are at increased risk of suicide attempt.^{28,29} It is interesting to note that this result is similar to that obtained by Kangelaris et al., which reported that hopelessness was significantly associated with the 5-HTTLPR "S" allele, regardless of the diagnosis of depression, concluding that the bearer of this allele may increase the susceptibility to develop this symptom.³⁰

While the results obtained do not demonstrate a significant association between the studied gene and the suicidal behavior, the association found between the "SS" genotype with the number of suicide attempts and hopelessness, as well as the presence of variables such as loss of appetite, weight loss and rejection sensitivity in the group with suicide attempts, could confirm the existence of a group of adolescents with a subtype of major depression and who are carriers of the "S" variant of the serotonin transporter.

Finally, we should mention that the main limitation of our study was the size and selection of the sample, so the findings reported in this study should be taken as preliminary until they are replicated in a larger sample. Similarly, it is possible that, because association studies are liable to present problems of population stratification, we could find a false-positive result, but it is interesting that the allele frequencies observed in our study are similar to those reported in an epidemiological study of Mexican adolescents.³¹ In future studies it will be necessary to perform the analysis of this or other genetic variants in larger samples, in an attempt to clarify the possible role of this gene in suicidal behavior.

CONCLUSION

Although today adolescent suicide is a major public health problem, genetic studies in this regard remain being scarce. This study increases the information on suicidal behavior among Mexican adolescents, correlating clinical features with a specific genotype.

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