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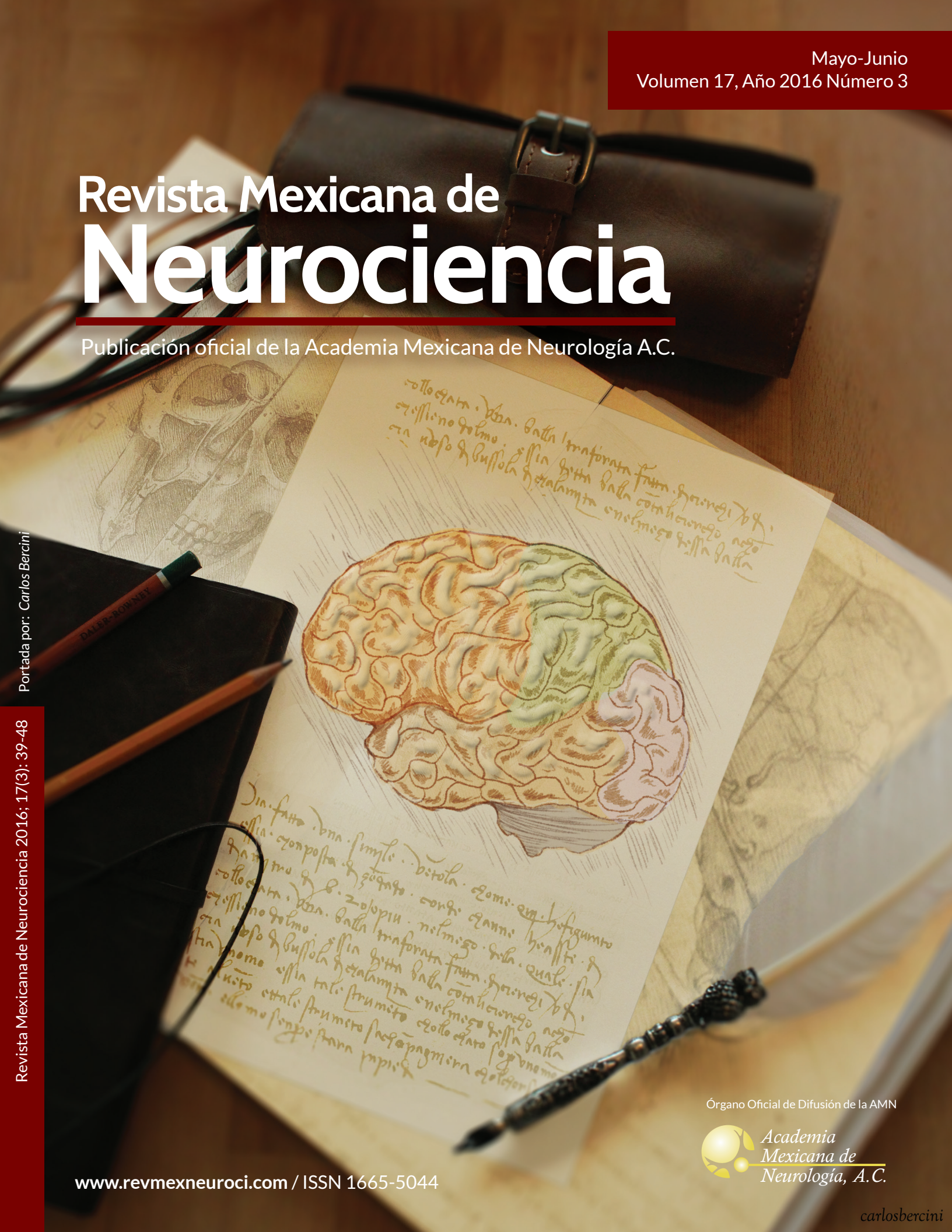

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Contribución Original

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Caracterización neuropsicológica del TDAH con ansiedad y su asociación de polimorfismos de un solo nucleótido del gen DGKH en una población pediátrica

Neuropsychological characterization of ADHD with anxiety, and its association of single-nucleotide polymorphisms of the DGKH gene in a pediatric population

Resumen

Introducción: El trastorno por déficit de atención e hiperactividad (TDAH) es uno de los trastornos psiquiátricos más frecuentes en niños. Ha sido identificado que el 60% de estos pacientes padecen de otras comorbilidades como desórdenes de aprendizaje y desórdenes afectivos, ansiedad, tics, trastorno obsesivo-compulsivo y otras conductas. La presencia de polimorfismos en el gen DGKH ha sido descrito en desórdenes afectivos, esquizofrenia y TDAH, esto ha llegado a ser un foco de atención en los análisis de funcionalidad de algunos mecanismos prefrontales.

Objetivo: Llevar a cabo la caracterización neuropsicológica de una muestra de niños y adolescentes de Colombia con TDAH y trastorno de ansiedad (TA) y explorar una posible asociación con dos polimorfismos (rs1170169 and rs9525580) del gen DGKH.

Materiales y métodos: Fueron incluidos 30 casos diagnosticados con TDAH y TA, 29 pacientes con TDAH sin otra comorbilidad y 33 controles. Para la búsqueda de la asociación con polimorfismos se utilizó PCR. Los análisis se realizaron a través de métodos bioinformáticos y estadísticos.

Resultados: Los niños diagnosticados con TDAH y TA tuvieron menor desempeño cognitivo, comparados con el grupo sin TA y el grupo control. El polimorfismo de un solo nucleótido (SNP) rs1170169 se encontró como protector para pacientes con TDAH y TA, así como para el grupo con TA, pero sin TDAH (OR: 0.39, 95% CI: 0.198–0.6873; p=0.01097). También identificamos que el SNP rs9525580

estuvo asociado con TDAH sin otra comorbilidad (OR: 2.5, 95% CI: 1.191–5.248; p=0.01).

Conclusiones: Polimorfismos en el gen DGKH están asociados tanto con fenotipos del TDAH solo, como con el TDAH más otras comorbilidades. Este estudio contribuye a la comprensión de la relación gen-ambiente en los niños con TDAH.

Palabras clave

Caracterización neuropsicológica, comorbilidad, gen DGKH, polimorfismos, trastorno de ansiedad, trastorno por déficit de atención e hiperactividad

Abstract

Introduction: The attention deficit hyperactivity disorder (ADHD) is one of the most frequent psychiatric disorders in children. It has been identified that 60% of patients have comorbidity with other disorders such as learning disorders, anxiety, affective disorders, tics, obsessive-compulsive disorders, and other behavior. The presence of polymorphisms of the DGKH gene has been described in affective disorders, schizophrenia and ADHD, becoming a focus of attention in the analysis of the functioning of some prefrontal mechanisms.

Objective: To conduct a neuropsychological characterization of comorbid ADHD patients with anxiety disorder (AD) and to explore a possible association of two common polymorphisms (rs1170169 and rs9525580) of DGKH gene, in a sample of school children and adolescents from Colombia.

Material and methods: A total of 30 diagnosed cases with ADHD and AD were included, as well as 29 patients with ADHD without comorbidity and 33 controls. For the association of polymorphisms, the technique used was a standard PCR and the respective analyzes were performed through bioinformatics and statistical methods.

Results: Children diagnosed with comorbid ADHD with AD had a low cognitive performance globally. This difference is significant, compared to the group without comorbidity and the control group. The single nucleotide polymorphism (SNP) rs1170169 was found to be significantly protective for patients with comorbid ADHD with AD as well as for the AD group without the disorder (OR: 0.39, 95% CI: 0.198–0.6873; p=0.01097). On the other hand, we identified that the gene variant rs9525580 was associated with ADHD without comorbidity, as compared with controls (OR: 2.5, 95% CI: 1.191–5.248; p=0.01).

Conclusions: Common gene polymorphisms of the DGKH gene may be associated with both ADHD and ADHD with comorbidities phenotypes. This study adds to the understanding of gene-environment relationship in children with ADHD.

Keywords

Anxiety disorder, attention deficit hyperactivity disorder, comorbidity, DGKH gene, neuropsychological characterization, polymorphisms

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Introduction

According to studies, in Colombia the prevalence of attention deficit hyperactivity disorder (ADHD) is around 16% of the general population likely to be increasing as it has been identified that there are risk factors such as extreme poverty, family breakdown, violence and low coverage of public services, etc., that may generate an increase in this disorder and have high prevalence in our environment. There are no statistical data on ADHD with anxiety disorder (AD) in Colombia, however, according to international research, it is estimated that about 47% of the total population affected with ADHD also have AD.[1-7]

ADHD genetic background

ADHD clinical studies have concluded that 15% of children with ADHD also have a parent with the disorder. Additionally, its prevalence is higher than 57% among children of parents with ADHD compared with families where it is not identified, which makes evident a possible pattern of inheritance. However, being a complex disorder, it is difficult to detect genetic functionality in its development, especially when a gene-environment dynamic is likely. So far, it is conclusive that there is a close relationship with such genes that express proteins of the dopaminergic system, which is why the pharmacotherapy for this disorder has focused on this route.[8-12]

DGKH gene

The DGKH gene expresses a protein called diacylglycerol kinase eta, which is part of the interneuronal communication process, signaling pathways associated with the dynamics of neurotransmitter regulation (catecholamine) and axonal growth.[13-15] Diacylglycerol kinases (DGKs) are a group of ten enzymes (DGKalpha, DGKbeta, DGKgamma, DGKdelta, DGKepsilon, DGKzeta, DGKeta, DGKtheta, DGKiota and DGKappa) that metabolize diacylglycerol (DAG) to produce phosphatidic acid (PA) and maintain intracellular concentrations of diacylglycerol. DGKs are widely distributed in tissues of mammals and its isoenzymes are present in different parts of the cell, where, according to their distribution in organelles, they have a specific role in modulating the levels of DAG in the translation of different routes of signaling including PKC (protein kinase C). This protein is directly involved in the regulation of catecholamines, in the prefrontal cortex, and it has been a research focus for future pharmacological therapies of some mental disorders, as the inactivation of this gene disrupts the regulation of norepinephrine, an essential neurotransmitter in the mechanisms of the prefrontal cortex in the control and regulation of behavior.[14,16-18]

Materials and methods

Inclusion criteria were: children between 7 and 14 years old, with established diagnosis according to the DSM-IV-TR criteria for attention deficit disorder and hyperactivity. The clinician collected the information from teachers and parents by using a SNAP questionnaire. To determine the comorbidity of the anxiety disorder, the clinician relied on the results of the STAIC and SCARED questionnaires children over 8 years. Children under 8 years were evaluated with the Achenbach scale. To identify the overall intellectual capacity and discard possible disabilities in such field, a progressive matrices test called RAVEN was used. The signature of the informed consent by the legal representatives of minors and their approval (informed assent) were given by the participants.

Procedure

Neuropsychological characterization

d. An assessment protocol was designed which evaluated: perceptual, executive and constructional skills, attention, memory and language (comprehensive and expressive) writing, mental and written calculations. For this purpose, the ENI (Evaluación Neuropsicológica Infantil) (Neuropsychological Assessment of Children) test battery and Raven's Progressive Matrices were used.[18]

e. Neuropsychological profiles were built by using

the statistical scores and the results obtained, to generate a table of values and a graphic profile.

f. Descriptive statistics and association analyzes were performed through the construction of a database with bioinformatic tools such as PLINK and statistical software such as Minitab and the Excel tools.[19,20]

g. The information obtained from the conceptual and empirical frameworks was revisited, described and compared with such found in the literature. Conclusions on the performance of participants with ADHD (with and without anxiety disorder) were given.

h. Results of the research process itself were provided, as well as suggestions for future research in the focusing area.

Genetic analyses

a. Single nucleotide polymorphisms (SNPs) were selected from the DGKH gene. By means of a literature review, it was found that rs9525580 and rs1170169 SNPs were highly associated with ADHD.21

a. Three primers were designed for each of the variations. For doing this, the Primer3 software was used. The possible harpin formation for each primer was analyzed as well as the possible dimers formation between primers by using the OligoAnalyzer software.[22,23]

a. A sample of saliva was taken in a falcon tube. Asking kids to rinse their mouths with moutyhwash. The extraction, purification and DNA testing were performed. For this purpose, the Quick-gDNA™ extraction kit was used.

a. Normal PCR amplification was conducted. To do this, a process of standardization where proper conditions were identified was performed.

a. Amplification was verified by using SYBR Safe® DNA-stained and UV visualized agarose gels.

a. Once standardized, the procedure was applied to the research participants.

a. The analysis of allele frequencies and genotypes were made with the help of computer programs for statistical analysis, as PLINK and Minitab.[20,21]

Results

Neuropsychological results

The results of the descriptive statistics of all the applied tests are shown in *table 1*.

In general, it was found that the group means of ADHD with anxiety disorder are much lower compared to the other groups in 90% of the cognitive tests.

When observing a general outcome of the global intellectual capacity from Raven's progressive matrices test, it was found that the group mean of comorbidity is much lower than the other groups. However, it was considered to observe the concentration of data among groups, which also was much lower compared to the other groups as shown in *figure 1*.

Genetic analysis

To identify whether the SNPs were in balance or not, the PLINK software was used. Two groups for analysis were made. The results are shown in *table 2*. Shaded rows show those alleles that are in disequilibrium. In the SNP rs1170169 it can be noted that, in general, the groups of cases are balanced in contrast to the control groups. In the SNP rs9525580, however, the groups of cases were unbalanced compared to the control group. Regarding the comparison of the two sets, the data were fairly similar.

Association analysis

For the combination also the software PLINK was used and, in this case, three groups were made: first the association of the alleles and the groups was made on one side the control group and on the other the ADHD group with and without AD. The results are shown in *table 3*. Association of allele "C" was found, but as a general protector for the disorder. In this case, it is important to note that the p value must be less than 0.05. The association is evident if the OR value is higher than 1, at which point the allele becomes a risk to generate the disorder. However, if it is less than 1, it becomes

protector as in this case. Last association is done with the alleles from the control groups and ADHD without Anxiety disorder. Here, an association at risk is present, which is the allele "A" to ADHD but without comorbidity, with an OR value of 2.5.

Proceso Cognoscitivo	Pruebas	TDAH con Ansiedad			Control			TDAH		
		X	S	Mediana	X	S	Mediana	X	S	Mediana
Habilidades Construccionales	Fig. Humana	7,90	2,454	8,000	9,78	2,619	9,000	8,96	2,117	8,000
	C. Fig. Com	8,83	3,405	9,000	10,78	2,434	10,00	9,58	3,571	10,00
Habilidades Perceptuales	Rec. de Exp.	9,63	2,895	10,50	10,51	2,451	11,00	10,03	3,065	11.00
	Int. de Ob.	10,03	3,449	10,50	11,30	3,147	11,00	10,20	3,579	9.00
Atención	Dig. en Pro	9,36	4,198	10,00	10,60	3,508	10,00	9,86	4,232	10.00
	Dig. en Reg	9,33	4,046	9,500	10,54	4,116	11,00	10,86	3,603	11.00
	Can. de dib.	5,83	2,276	6,00	7,97	2,856	8,000	8,31	2,634	8.00
Memoria	M.v. aud.	8,20	3,112	8,500	10,63	2,714	11,00	9,31	3,307	9.00
	M. Fig. Com	8,56	2,967	9,00	10,39	2,449	10,00	8,79	2,833	10.00
Lenguaje	Dic. Oraciones	10,93	2,599	11,00	13,60	1,749	14,00	10,72	2,776	11.00
	Cal. Ment	8,56	3,308	8,00	10,69	2,325	11,00	8,20	2,846	8.00
	Cal. Esc.	8,73	3,016	9,00	11,87	2,595	12,00	10,82	2,331	11.00
	Coh. Narr	6,66	3,021	7,00	11,03	2,481	10,00	7,93	3,751	7.00
	Long. Exp.	6,33	2,796	6,00	10,09	2,283	10,00	7,41	2,626	7.00
Funciones Ejecutivas	Fl. No sem	6,46	1,978	6,00	10,97	2,840	11,00	8,13	2,601	8.00
	F.c. Ensadm	7,36	1,066	7,00	8,818	2,270	8,00	8,13	1,575	8.00
	F.c. rtacorr	7,26	3,903	7,50	9,273	2,820	9,00	7,34	2,511	8.00
	F.c. to erro	7,40	3,450	7,50	8,939	2,989	8,00	7,17	2,450	7.00
	F.c. de cat	8,23	2,825	7,50	9,788	2,446	10,00	9,86	2,216	11.00

Table 1. Descriptive characteristics of patients with ADHD, ADHD with anxiety disorder and control.

Hardy–Weinberg equilibrium control group and ADHD with comorbidity								
CHR	SNP	TEST	A1	A2	GENO	O(HET)	E(HET)	P
13	DGHKrs1170169	ALL	C	G	13/56/22	0.6154	0.4951	0.03346
13	DGHKrs1170169	AFF	C	G	5/32/21	0.5517	0.462	0.2526
13	DGHKrs1170169	UNAFF	C	G	8/24/1	0.7273	0.4775	0.004069
13	DGKHrs9525580	ALL	A	G	23/25/40	0.2841	0.4813	0.0001362
13	DGKHrs9525580	AFF	A	G	17/15/23	0.2727	0.494	0.0009651
13	DGKHrs9525580	UNAFF	A	G	6/10/17	0.303	0.4444	0.1101
Hardy–Weinberg equilibrium control group and ADHD without comorbidity								
CHR	SNP	TEST	A1	A2	GENO	O(HET)	E(HET)	P
13	DGHKrs1170169	ALL	C	G	13/37/12	0.6066	0.5	0.1292
13	DGHKrs1170169	AFF	C	G	4/13/11	0.4643	0.4688	1
13	DGHKrs1170169	UNAFF	C	G	8/24/1	0.7273	0.4775	0.04069
13	DGKHrs9525580	ALL	A	G	18/16/26	0.2667	0.4911	0.0004975
13	DGKHrs9525580	AFF	A	G	12/6/9	0.2222	0.4938	0.005445
13	DGKHrs9525580	UNAFF	A	G	6/10/17	0.303	0.4444	0.1101

Table 2. Analysis of the Hardy–Weinberg equilibrium among groups.

Association analysis. Control vs. ADHD (general)					
SNP	**Associated allele**	**Chi-squared**	**P- value**	**OR**	**95% CI**
DGHKrs1170169	C	10.12	0.00147	0.3689	(0.198 – 0.6873)
DGKHrs9525580	A	2.155	0.1421	1.607	(0.8513 - 3.032)
Association analysis. Control vs. comorbidity					
SNP	**Associated allele**	**Chi-squared**	**P- value**	**OR**	**95% CI**
DGHKrs1170169	C	8.251	0.004073	0.35	(0.1696– 0.7224)
DGKHrs9525580	A	0.004811	0.9447	1.027	(0.4834 - 2.182)
Association analysis. Control vs. ADHD without comorbidity					
SNP	**Associated allele**	**Chi-squared**	**P- value**	**OR**	**95% CI**
DGHKrs1170169	C	6.47	0.01097	0.39	(0.1875– 0.8113)
DGKHrs9525580	A	5.973	0.01453	2.5	(1.191 - 5.248)

Table 3. Association analysis among groups.

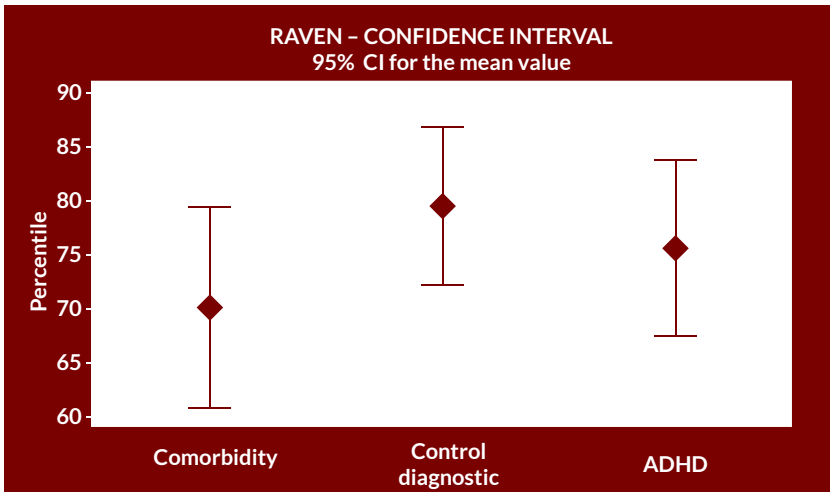

Figure 1. Raven test confidence interval.

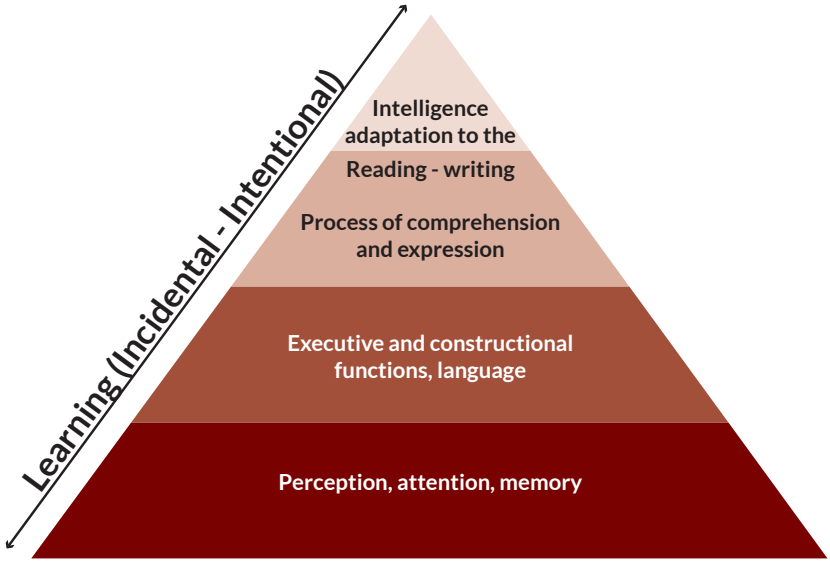

Figure 2. Pyramid of cognitive processes

Discussion

Neuropsychological Characterization

In this study it was found that ADHD and AD greatly increased the problematic in the whole child's psychological process, it is similar to the findings of a comparative study made by Willcutt and cols.25 about ADHD and dyslexia proper deficits. They identified that ADHD was associated with inhibition deficits, while dyslexia was associated with phonological awareness and working memory. When the two criteria were unified ADHD and dyslexia in children, it showed important alterations in all these functions, it means that its clinical picture was negatively strengthened.[24,25] Similarly, studies that only have deepened in anxious children with neuropsychological deficits have found that the majority presents learning difficulties. However, they also identified that this fact was secondary to a shrinkage response that the child assumed to face—in his opinion—an aggressive environment. This behavior carries the child to a new learning acquisition dysfunction. Furthermore, intrusive phenomena were identified, for example, the same disorder symptomatology that favors distractibility.[26]

Studies have deepened in the reasons why this type of problematic occurs; they have agreed that AD reduces the psychosocial possibilities because in one hand it reduces coping skills for problems and interferes in the functional learning processes and thus, cognitive processes are disturbed. In the other hand, studies suggest that the major incidence is due to difficulties related to incidental learning, which is the one that takes place in a natural and implicit way.[27] Incidental learning is the result of human activity from interactions, the acquisition of the customs and beliefs of the same culture, and of the trial and error; aspects generated in daily life, which additionally may occur in formal and informal fields. Brain plasticity is also highly attributed to incidental learning. It is to say, people who present anxiety disorder tend to be more rigid to the environment, so, their incidental learning process decreases[27,28]

It has been constantly noted that human being creative activity is directly related to a variety of wealth of the gained experience by the human being itself, because this experience is the tool human beings have to build many things to constantly revolutionize society in a creative way.[29] It means that when an anxiety disorder is present, it reduces the interaction with the surrounding; therefore, the person decreases the interaction with himself. Furthermore, in this study the cognitive processes analysis, from the simplest to the most complex, evidenced that children from the control group had difficulty since the simplest cognitive processes compared to the ADHD group which showed difficulty just in executive functions and specifically in inhibition. The figure 2 shows how the cognitive processes are given, from the simplest, at the base, to the most complex in their neurodevelopmental formation process. A pyramidal design was made because each level is a support to the next and it could be constituted in quality levels, it is to say that it could be good, regular or bad, or simply there is absence. This is the reason why the percentage--in terms of learning difficulties--was statistically significant for the two groups because it is where all the cognitive skills work. According to this study, ADHD and AD group had more significant and complex learning difficulties, 83% of these children had difficulties compared to the ADHD group that was 43%. At some point, this analysis may reconfirm that anxiety does importantly influence in the child´s cognitive development and its interference is present since the simplest cognitive processes.[30]

Genetic Association

It is important to make clear that the sample was small to generalize these results; however it was necessary to establish a pilot study to see the existence of these genetic markers in the Colombian population and make an approach to their possible association to the disorder.[8,9,31-34] References to these genetic markers belonging to DGKH gene do not exist in Latin-America, and in terms of child population, they do not exist around the world; the only existing association of these types is the ones detected in Germany where as

a result, there was an association with affective disorders and ADHD.[15]

When the analysis to both SNPs was made to know whether they were in balance or not, at the moment of comparing ADHD and AD group with the control group, it was especially found that in the SNP rs1170169 the control group allele was in imbalance, this may happen because of two reasons: an inadequate genotypification or a bias in the sample; in this case it was considered that it happened because of the second reason as the sample number was not enough. Even so, it is important to take into account that this could be considered as a tendency because of other two reasons. In terms of phenotype, Colombia has the higher percentage of people who present the disorder, while in other countries it is around 7%. On the other hand, the odds ratio of that SNP evidenced to be a characteristic of nature evolution.[35,36]

According to the question whether a genetic association with the disorder existed or not, it can be stated that the results show a similar pattern to the ones found in the German study, which is the only existent study about these SNPs. This research showed that the alleles of lower frequencies were associated to ADHD among other disorders. The SNP rs9525580 only had an association at risk to ADHD without AD. It is probable that these findings confirm that the clinical pictures of the two groups are different, so there are two different disorders.[37-39] Briefly, the alteration in ADHD is just from the inhibition deficit as part of the identified functions in the prefrontal area where -as it was mentioned before- it has been identified that the DGKH gene seems to have interference in the regulation of the catecholamines.

Conclusions

Within the neuropsychological characterization, the interest group, ADHD with AD shows a lower cognitive performance compared to the ADHD group. It is probable that the AD might act as a persistent interference in the intellectual capacity and adaptability to the environment. The findings showed that the neuropsychological characterization of the disorder groups is different among them. The ADHD with AD group demonstrated a lower cognitive performance in general, while the ADHD group evidenced an inhibition alternation as part of the executive function. It is possible that the symptoms of ADHD are a manifestation of AD and reiterates that the AD symptomatology produces an inability to resolve the requirements of the environment, especially the ones from school.

In the patients with ADHD without AD presented a significant association at risk with the SNP 9525580 of the DGKH gene. This same group was especially characterized by showing an inhibition alteration as part of the executive function, which is also localized in the prefrontal cortex, however it should be considered to broaden the sample in order to corroborate this association. A significant statistically association of the SNP 1170169 belonging to DGKH gene was identified to the disorder as a protector of the ADHD development, however to broaden the sample should be considered to corroborate this association.

Conflict of interest

The author first, author of the manuscript reference, in their name and in that of all the signatories authors declare that there is no potential conflict of interest related to the article.

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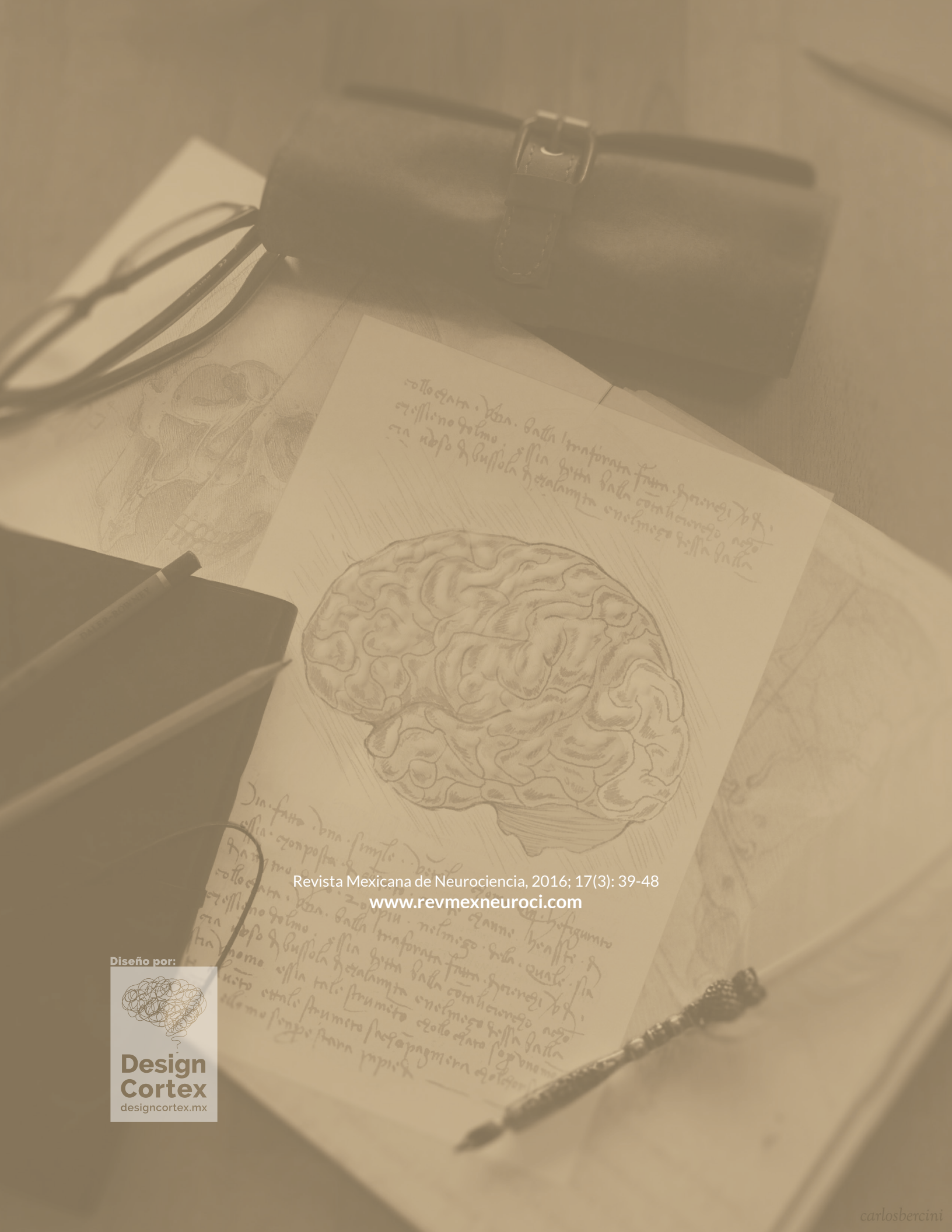

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