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Common genetic aspects between Autism Spectrum Disorder and Attention Deficit Hyperactivity Disorder: integrative review

Aspectos genéticos comuns entre o Transtorno do Espectro Autista e Transtorno do Déficit de Atenção e Hiperatividade: revisão integrativa da literatura

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Abstract

Objective: The selected studies were analyzed descriptively regarding the common genetic etiology of autism spectrum disorder and attention deficit hyperactivity disorder, allowing for observing, describing, and classifying the data. **Methods:** We performed a review of the literature on Pubmed and Virtual Health Library (VHL) databases. The search descriptors (Autistic Disorder) OR (Autism Spectrum Disorder) AND (Deficit Disorder) of Attention with Hyperactivity) AND (Genetic Association Studies) OR (Genetics) OR (Heredity) were used in VHL; and ((“Autism Spectrum Disorder” AND “Attention Deficit Disorder with Hyperactivity”) AND (“Genetic Association Studies” OR “Genetics OR Heredity”)) were used in PubMed. **Results:** A total of 75 studies were identified, 54 in the VHL and 21 in the PubMed. Of these, 18 remained after screening for title and abstract. After full text reading, nine studies were included in this review. **Discussion**: De novo genic mutations contribute to autism spectrum disorder, and some studies support they might also be determinant for attention deficit hyperactivity disorder. The RFX3, RFX4, and RFX7 genes found in cells of the cerebral cortex of fetuses and adults contribute to linking important regions related to cognition and social behavior. **Conclusion:** The included studies indicate a correlation between genetic etiologies of autism spectrum disorder and attention deficit hyperactivity disorder.

Keywords: Autism Spectrum Disorder; Attention Deficit Hyperactivity Disorder; Mutations; Genes.

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Resumo

Objetivo: Os estudos selecionados foram analisados descritivamente quanto à etiologia genética comum do transtorno do espectro autista e do transtorno de déficit de atenção e hiperatividade, permitindo observar, descrever e classificar os dados. **Métodos:** Foi realizada revisão da literatura nas bases de dados Pubmed e Biblioteca Virtual em Saúde (BVS). Os descritores de busca (Autistic Disorder) OR (Autism Spectrum Disorder) AND (Deficit Disorder) of Attention with Hyperactivity) AND (Genetic Association Studies) OR (Genetics) OR (Heredity) foram utilizados na BVS; e ((“Autism Spectrum Disorder” AND “Attention Deficit Disorder with Hyperactivity”) AND (“Genetic Association Studies” OR “Genetics OR Heredity”)) foram usados no PubMed. **Resultados:** Foram identificados um total de 75 estudos, 54 no BVS e 21 no PubMed. Destes, 18 permaneceram após a triagem para título e resumo. Após a leitura do texto completo, nove estudos foram incluídos nesta revisão. **Discussão:** Mutações gênicas de novo contribuem para o transtorno do espectro do autismo, e alguns estudos apoiam que elas podem também ser determinante para o transtorno de déficit de atenção e hiperatividade. Os genes RFX3, RFX4 e RFX7 encontrados em células do córtex cerebral de fetos e adultos contribuem para ligar regiões importantes relacionadas à cognição e ao comportamento social. **Conclusão:** Os estudos incluídos indicam uma correlação entre fatores genéticos

Palavras-chave: Transtorno do Espectro Autista; Transtorno de Déficit de Atenção e Hiperatividade; Mutações; Genes.

INTRODUCTION

Neurodevelopment disorders encompass multiple conditions affecting cognitive development. Two of the most common neurodevelopmental disorders are autism spectrum disorder (ASD) and attention deficit hyperactivity disorder (ADHD)[1]. The ASD leads to deficits in social interaction and communication and is associated to repetitive behaviors and restricted interest to specific topics[2]. In turn, ADHD is characterized by hyperactivity, lack of attention, and impulsivity 3 . In some situations, the two disorders present clinical and genetic overlap, including attention deficit, impulsiveness, delay in language development, communication problems, and difficulties in understanding the thoughts and feelings of other people, accomplishing tasks every day, coping with emotional aspects, and adapting to environments like schools[4].

The ADHD prevalence in children at age school is about 5%, whereas the ASD prevalence varies from 1% to 2%[5]. Both disorders are hereditary, more frequent in males, and associated with lower quality of life[2]. ADHD might occur simultaneously with ASD in 22% to 83% of cases, while ASD might occur simultaneously with ADHD in 30% to 65% of cases. Approximately 20% of ASD diagnoses happen after three years of ADHD diagnosis[4].

Although ASD and ADHD are genetically heterogeneous disorders, a person with both disorders may show alterations in independent genes or common genetic mutations[6]. Common genetic mutations usually present allelic forms of risk shared in non-coding areas of the genome, affecting gene expression regulation[4]. However, de novo genetic variants (i.e., new genes not inhe-

rited from the parents due to various etiologies) culminating in haploinsufficiency are reported as contributors to this comorbidity[2]. An example includes the deleterious variants in the RFX genes, specifically RFX3, RFX4, and RFX7, involved in central nervous system development and ciliogenesis[7]. Another possible etiology for this comorbidity encompasses changes in the SLC9A9 gene, a gene involved in many cellular functions and associated with several human diseases. The main role of the SLC9A9 gene is to maintain the late endosomes recycling, sustaining the surface and the pool of signaling receivers. This gene is also important for cellular survival and neurological development[6].

This review investigated common genetic etiology between ASD and ADHD. The included studies were analyzed descriptively, allowing for observing, describing, and classifying the extracted data.

METHODS

A literature review was conducted in Virtual Health Library (VHL) and PubMed databases. The descriptors and booleans operators (Disorder Autistic) OR (Disorder of Spectrum Autistic) AND (Disorder of Deficit in Attention with Hyperactivity) AND (Studies in Association genetics) OR (Genetics) OR (Heredity) were used to search in the VHL database. The inclusion criteria were: main subject ASD or ADHD, and studies about disorder etiology, published in the last five years in English, Spanish, or Portuguese.

For PubMed database, the following descriptors and boolean operators were searched: ((“Autism Spectrum Disorder” AND “Attention Deficit Disorder with Hyperactivity”) AND (“Genetics Association Studies” OR “Genetics” OR “Heredity”)). The inclusion criteria were MEDLINE database, human species, classic articles, systematic review, and study with twins, published in the last five years in English, Spanish, or Portuguese. The exclusion criteria in both databases encompassed studies not addressing genetic aspects.

RESULTADOS

Initially, 75 studies were identified, 54 from the VHL and 21 from PubMed. Of these, 57 were excluded after screening for title and abstract. From the remaining 18 studies, nine were selected after full text reading to be included in this review, as described in Figure 1.

Relevant findings were rigorously interpreted, and the main themes were selected and 38 transformed into a table with the summary of the analyzed criteria (Table 1).

Figure 1. Flow diagram for this integrative review.

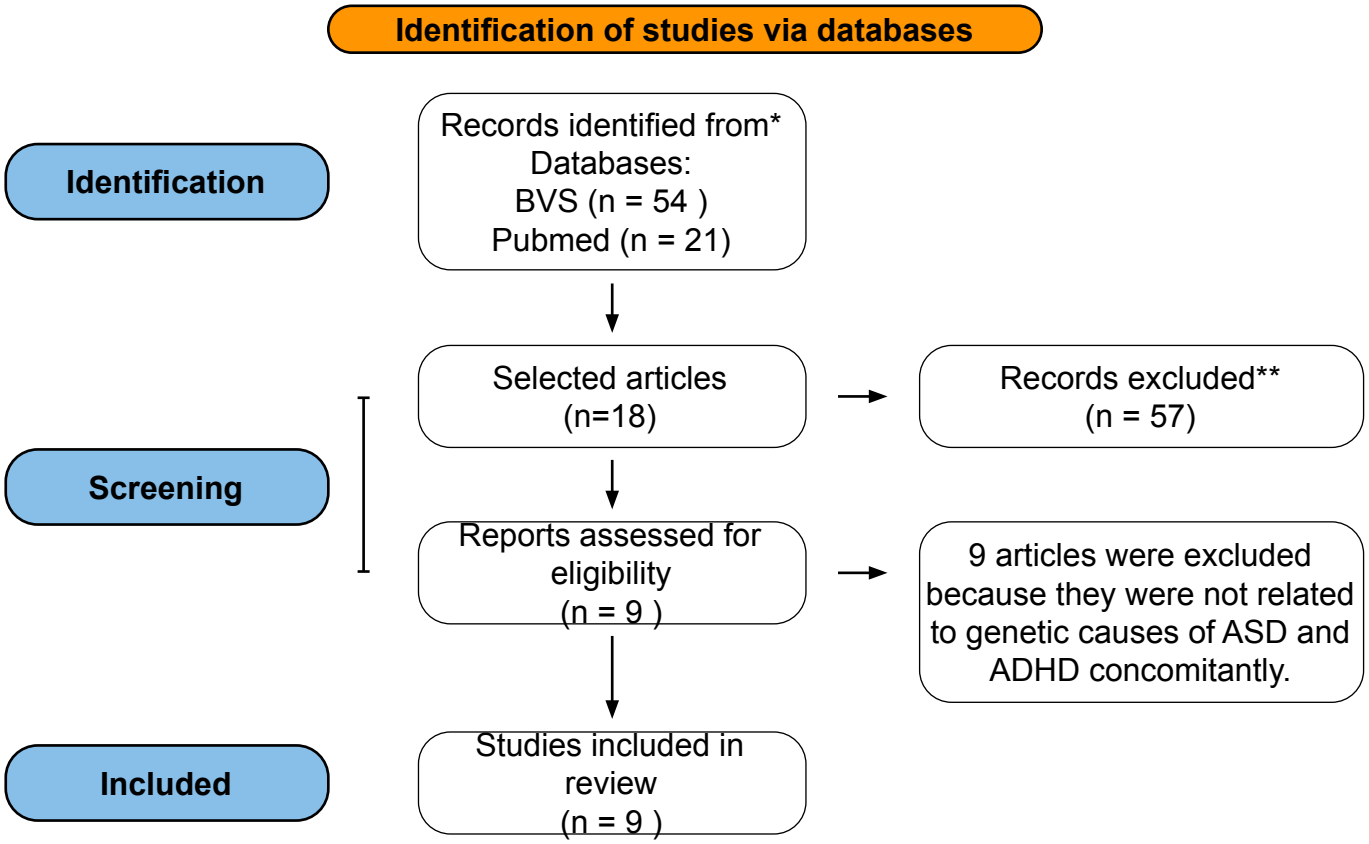

Table 1. Summary of the main findings from the included studies

Title	Author/ Year	Objective	Results	Conclusion
Early environmental risk factors for neurodevelopmental disorders - a systematic review of twin and sibling studies.	Carlsson T. et al., 2021.	To summarize the evidence from studies with twins and family members about the role of environmental risk factors for developmental disorders, defined both dimensionally and categorically, controlling for familial confusion to inform research and funding agencies in preclinical and applied areas of developmental disorders, and guide clinical management.	A total of 140 studies were identified for inclusion. The search resulted in 7,315 unique citations. Two additional studies were identified from reference lists of published articles. After screening the abstracts, 7,061 citations were excluded.	Beyond familial confusion, advanced paternal age, low birth weight, complications at birth, perinatal hypoxia, and respiratory stress are consistently associated with the diagnosis of ASD; low birth weight, gestational age, and low family income or transient decline in income during childhood are associated with ADHD, both categorically and dimensionally.

Disruption of *RFX* family transcription factors causes autism, attention-deficit/hyperactivity disorder, intellectual disability, and dysregulated behavior.	Harris HK., et al. 2021	To describe a new neurobehavioral phenotype in ASD, deficiency intellectual, or ADHD associated with deleterious de novo variants or inherited in genes RFX family members	These individuals share neurobehavioral characteristics, including ASD, intellectual disability, or ADHD. Other common features include hypersensitivity to sensory stimuli and sleep problems. RFX3, RFX4, and RFX7 are strongly expressed in the developing and adult human brain, and X-box binding motifs are enriched in the cis-regulatory regions of known risk genes for ASD, similar to RFX ChIP-seq peaks.	The results establish a role of deleterious variation in RFX3, RFX4, and RFX7 in deficiency intellectual monogenic, ADHD, and ASD. These genes can act as critical transcriptional regulators in neurobiological pathways associated with the pathogenesis of neurodevelopmental disease
Attention Deficit/ Hyperactivity Disorder and risk for non-affective psychotic disorder: The role of ADHD medication and comorbidity, and sibling comparison.	Björkenstam. et al, 2020.	To include a paired cohort composed of all people born in Sweden between 1987 and 1991.	The paired cohort included 18,139 individuals with ADHD and 72,437 without exposure. Parents of individuals with ADHD had more history of psychiatric disorders and less favorable socioeconomic characteristics than control parents. A total of 26% of individuals with ADHD had comorbid substance abuse (but only 5% in controls), of which the most common was alcohol-related disorders (11.9% of individuals with ADHD versus 3.3% in control).	Individuals with ADHD have a markedly increased risk for non-affective psychotic disorder, and the risk is partially explained by comorbid ASD and or both substance abuse. Among individuals with ADHD, using stimulant or non-stimulant medications is associated with an increased risk of NASD, indicating that the clinical symptoms that lead to medication treatment in ADHD may also increase the risk of NAPD.
Examining the autistic traits in children and adolescents diagnosed with attention-deficit.	Okyar E., Görker I., 2020.	To examine the symptoms of ASD in children diagnosed with ADHD and their parents. Also, to investigate the parental risk factors that increase ASD characteristics in children. Lastly, the risk factors related to pregnancy, birth, and development history were examined.	More symptoms of autism were found in children diagnosed with ADHD than in the control group. More autistic symptoms were perceived in males, and the presence of oppositional defiant disorder (ODD). Although more ADHD symptoms were observed in parents of children diagnosed with ADHD, it did not differ from parents in the control group.	ASD and ADHD have high levels of comorbidity. The etiology remains uncertain. Both ADHD and ASD show strong hereditary transitions. Maternal and paternal ADHD symptoms predicted autism in children with ADHD. However, more studies are needed to reveal the etiology.

Early-life antibiotic use and risk of attention-deficit hyperactivity disorder and autism spectrum disorder: results of a discordant twin study.	Slob Em., et al. 2021.	To evaluate the association between the use of antibiotics at the beginning of life and the risk of developing ADHD or ASD, controlling genetic and environmental factors shared in a project of discordant twins.	The use of antibiotics at the beginning of life was associated with an increased risk of developing ADHD [OR = 1.10, 95%CI:1.02-1.17] and ASD (OR = 1.15, IC 95%:1.06 - 1.25) in a project case-control.	The findings suggest that the association between early-life antibiotic use and the risk of ADHD and ASD may be confounded by shared family environment and genetics.
Sodium hydrogen exchanger 9 NHE9 (*SLC9A9*) and its emerging roles in neuropsychiatric comorbidity.	Patak J., Faraone Sv., Zhang-James Y., Et Al. 2020	To summarize the current literature regarding the structure, function, and disease associations of SLC9A9, and provide a comprehensive analysis of the role of SLC9A9 in human pathology.	We examined the structure of the SLC9A9 protein by homology-based comparison and summarized the biochemical mechanism that drives Na+/H+ exchange in homologs with the most conserved sequences.	The SLC9A9 is a multifunctional protein that, by its regulatory function of endosomes and its protein-protein interaction network, may modulate signaling axes, such as the PI3K pathway.
Cis-effects on gene expression in the human prenatal brain associated with genetic risk for neuropsychiatric disorders.	Hall Ls., Et Al. 2021	To define the genetic predictors of gene expression in the fetal human brain in studies analyzing wide association of ADHD, ASD, bipolar disorder, depression disorder, and schizophrenia Transcriptome.	Identify the effects of prenatal cis-regulatory in 63 genes and 166 individual transcribed associated with the genetic risk for these conditions.	The findings support that altered gene regulation in the prenatal brain increases the susceptibility to several neuropsychiatric disorders and prioritizes potential risk genes for further neurobiological investigation.

Mutations associated with neuropsychiatric conditions delineate functional brain connectivity dimensions contributing to autism and schizophrenia.	Moreau Ca., et al. 2020	To characterize the functional connectivity (FC) signatures of four high-risk neurodevelopmental copy number variants (CNV), explore whether the FC signatures of CNV represent dimensions observed in idiopathic ASD, schizophrenia, or ADHD, and investigate the relationship between gene expression level deletions and FC.	The 16p11.2 deletion showed an overall increase in FC compared to controls with a mean deviation = 0.29 z-scores ($p = 0.048$). 88 significantly altered connections (FDR, $q < 0.05$), and all but one were hyperconnected with beta values ranging from 0.76 to 1.34 z- scores. Hyperconnectivity involves the frontal, somatomotor, ventral attention, and basal ganglia networks AD neuropathology and an increased prevalence of amyloid angiopathy brain (AAC). The phenotypic features of DS do not appear to occur in individuals with dup-APP. Although almost all individuals with DS have AD neuropathology, the variability in the prevalence of dementia is more pronounced in DS than in dup-APP, while AAC is less prevalent in DS than in dup-APP. These differences between DS and dup-APP phenotypes provide a better understanding of the roles genes on chromosome 21, other than APP, may have in the pathogenesis of AD.	Individuals with greater similarity to functional connectivity deletion signatures exhibit worse cognitive and behavioral symptoms. Exclusion similarities identified at the connectivity level may be related to the redundant associations observed across the genome between spatial patterns of gene expression and signatures of functional connectivity. The results may explain why many CNV affect a similar range of symptoms in neuropsychiatrics.
Polygenic risk scores for major psychiatric and neurodevelopmental disorders contribute to sleep disturbance in childhood: Adolescent Brain Cognitive Development (ABCD) Study.	Ohi K., et al. 2021.	Investigated whether polygenic characteristics of psychiatric and neurodevelopmental disorders are associated with sleep disorders during childhood.	ADHD symptoms were weakly to modestly correlated with sleep disturbance scales ($p < 0.001$), particularly sleep initiation and maintenance disorders and excessive sleepiness disorders. Preliminarily performed genome-wide association studies using sleep disturbance scale total scores in children of European ancestry and children of trans ancestry.	The findings further confirmed that genetic vulnerabilities to ADHD, major depressive disorder, and anxiety disorders positively correlate with sleep disorders in childhood.

Legend: OD, odds ratio; ASD, autism spectrum disorder; ADHD, attention deficit hyperactivity disorder; NAPD, non-affective psychotic disorder; ODD, oppositional defiant disorder; DD, developmental disorders; AAC, amyloid angiopathy brain; CNV, Copy Number Variants; FC, functional connectivity; CI, confidence interval; GWAS, genome-wide association studies; FDR, False Discovery Rate; p, p-value; APP, amyloid precursor protein; DS, Down syndrome; MDD, major depressive disorder.

DISCUSSION

Autism spectrum disorder and attention deficit hyperactivity disorder are neurodevelopmental disorders that may coincide clinically and genetically. Both disorders may originate from independent genes or the same genetic mutation[1,4].

De novo genic mutations contribute to ASD, and some evidence demonstrates its contribution to ADHD[2]. The RFX transcription factors demonstrated regulatory function in genes involved with several cellular processes related to human development, e.g., cellular cycle, DNA repair,and cellular differentiation[7]. The RFX3, RFX4, and RFX7 genes are found in the cerebral cortex cells of fetuses and adults and contribute to communicating important regions for cognition and social behavior. In adults, the RFX3 and the RFX7 are expressed in neurons from the layer glutamatergic 2/3 and in inhibitory and excitatory neurons, respectively, whereas the RFX4 was mostly described in astrocytes[2]. In contrast with the RFX genes, the SLC9A9 gene is a member of the genetic family expressing proteins that are Na+/H+ exchangers. This gene has 16 exons in the long arm of chromosome 3 (AUTS16 locus), and its dysfunction leads to diseases including cancer and neuropsychiatric disorders, such as ASD and ADHD. Due to its role in regulating the pHj of the endosomal system and assisting with the transport of iron, proteins, and synaptic regulation, a dysfunction impacts several cellular functions[6].

One study published in 2021 and conducted with 38 individuals diagnosed with intellectual disability (ID; ASD and or both ADHD) from 33 families revealed the presence of different deleterious de novo mutations among participants, except for one parent. This parent transmitted the de novo mutation RFX3 to his three children and three other homozygous brothers who shared the same gene for one missense variation of RFX4. Of the 18 individuals carrying RFX3 variants, 72% had ASD, and 56% had ADHD. Fourteen individuals carrying variants RFX7 also presented ASD (36%) and or both ADHD (29%). The conclusion was that the neurobehavioral phenotypes of all individuals were very similar, reinforcing the previous evidence that RFX3 is a risk gene for ASD. Furthermore, this conclusion was extended to other genetic families, such as RFX7. This genetic family was not previously associated with human diseases and can possibly contribute to ADHD[2].

The SLC9A9 is likely related to autistic phenotypes due to the strong correlation to changes in synapses genetic expression. An analysis performed in rats showed that mutations in this

gene increased the interaction of the SLC9A9 protein with the macromolecule calcerin homolog, revealing a potential involvement in the production of inattentive phenotypes similar to those in rats with ADHD. In another study with rats, using C57/BI6 genetic models inducted to delete the exon 2 of the reported gene, results indicate the interruption of translation protein. As a result, similar traits to ASD were observed, such as reduced preference for social novelties, reduced vocalization ultrasonic, and increased time in self-cleaning. The centric inversion of chromosome 3 (p14:q21) could also terminate the expression of DOCK3 and SLC9A9 genes, responsible for phenotypes such as ID, inattention, and low intelligence coefficient. Therefore, the loss of the SLC9A9 function occurs frequently in ASD and ADHD[6].

One study analyzed the copy number variation (CNV), i.e., deletions or duplications of DNA segments representing an important basis for genetic heterogeneity, of 16p11.2 and 22q11.2. The authors found that CNV confers high risk for ASD, schizophrenia, and ADHD, as they affect functional connectivity, with twelve CNV individually associated with ASD and eight with ADHD. Although CNV has major impacts on neurodevelopment, their effect does not lead to a diagnosis. In this sense, the CNV knowledge may facilitate the identification of the main dimensions contributing to idiopathic conditions[8].

The SLC9A9 dysfunction in individuals diagnosed with ASD causes a pH reduction of astrocytic endosomes, physiologically changing the pan- receptor recycling and increasing the glutamate in the synapse. At the same time, a decrease in the uptake action of the GLAST transporter damages the excitatory and inhibitory system, predisposing to seizures and epilepsy, which are common in ASD[6]. Patterns of generalized subconnectivity were frequently demonstrated, except for the superconnectivity in cortico-subcortical connections, particularly involving the thalamus. This shared characteristic between ASD and ADHD appears to encompass several continuous dimensions related to the genetic commonalities between diagnoses, documented for common and rare variants, including the CNV of 16p11.2 and 22q11.2[8].

Genome-wide association studies with human fetuses of second quarter gestation demonstrated the main genes and transcripts with effects cis- regulatory (perform regulatory functions in genic expression at the same chromosome in determined sequence) of the most common neuropsychiatric illnesses. These studies highlight 63 genes and 166 individual transcripts for these conditions. For ADHD, expression predictors are associated with the expression of three genes and four individual transcripts in the fetal brain, whereas for ASD, 17 genes and 29 individual transcripts[9].

The literature shows that ASD is a clear risk factor for non-affective psychotic disorder, including schizophrenia. Differently is observed in the few studies relating ADHD to risk factors. A study of a paired cohort associated comorbid ADHD with ASD and explained the risk for non-affective psychotic disorder in individuals with ADHD. The study concluded that individuals with

ADHD had a higher risk of presenting non-affective psychotic disorder than controls. However, when individuals with ADHD were compared to those with ASD and ADHD comorbidity, the risk of developing non-affective psychotic disorder was smaller in individuals with comorbidity, although the result was quite significant[3].

CONCLUSION

According to the included studies, there is a genetic etiological relationship between ASD and ADHD. The dysfunction of the RFX and SLC9A9 genes was responsible for the association between ASD and ADHD. In contrast, the CNV in 16p11.2 and 22q11.2, in addition to other genes and their transcripts with cis-regulatory effects, appear to contribute individually to these disorders. This review findings contribute to understanding the genetic aspects impacting the pathophysiology of ASD and ADHD. However, additional studies are needed to allow advances in diagnosis and treatments.

CONFLICT IN INTERESTS

None.

CONTRIBUTIONS OF THE AUTHORS

MMLM: main author; **JSM** and **JMSD**: co-authors; **HEEV** and **AESM**: Advisors.

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