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CYP2D6 polymorphisms in drug therapy in autism spectrum disorder (ASD) in children and adolescents

Polimorfismos da CYP2D6 na terapia medicamentosa no transtorno do espectro autista (TEA) em crianças e adolescentes

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ABSTRACT

Introduction: Autism spectrum disorder (ASD) impairs neuropsychomotor development, hindering cognition, language, and social interaction. It is genetic in origin, and severe behavioral symptoms related to it are currently treated with antipsychotics, primarily risperidone and aripiprazole.

Objective: To describe the influence of genetic polymorphisms of the CYP2D6 enzyme on the treatment with risperidone and aripiprazole in ASD.

Method: Electronic search from January 2023 to December 2023 in the main scientific databases, using combinations of MeSH/DeCS descriptors and free terms related to ASD ("Autism Spectrum Disorder", "Autism"), drugs ("risperidone", "aripiprazole"), clinical manifestations ("disruptive behavior", "irritability", "stereotypies"), and pharmacogenomics ("CYP2D6*3 and CYP2D6*4 alleles, "metabolizers").

Result: Seventy-two articles were included in Portuguese, English, and Spanish, published between 2010 and 2024.

Conclusion: ASD manifests itself in diverse ways, and understanding its clinical characteristics, drug treatment, and knowledge of drug pharmacogenetics is of great importance for adequate disease control and improved quality of life.

KEYWORDS: Autism spectrum disorder. Risperidone. Aripiprazole

RESUMO

Introdução: O transtorno do espectro autista (TEA) compromete o desenvolvimento neuropsicomotor, dificultando a cognição, linguagem e interação social. É de etiologia genética e atualmente, o tratamento de sintomas comportamentais graves relacionados a ele é realizado com antipsicóticos, principalmente com a risperidona e o aripiprazol.

Objetivo: Descrever no TEA a influência dos polimorfismos genéticos da enzima CYP2D6 no tratamento com risperidona e o aripiprazol.

Método: Busca eletrônica de janeiro/2023 a dezembro/2023 nas principais bases de dados científicas, utilizando combinações de descritores MeSH/DeCS e termos livres relacionados ao TEA ("Transtorno do Espectro Autista", "Autismo"), aos fármacos ("risperidona", "aripiprazol"), às manifestações clínicas ("comportamento disruptivo", "irritabilidade", "estereotipias") e farmacogenômica ("alelos CYP2D6*3 e CYP2D6*4, "metabolizadores").

Resultado: Foram incluídos 72 artigos nos idiomas português, inglês e espanhol, publicados entre 2010 e 2024.

Conclusão: TEA se manifesta de forma diversificada, e o entendimento de suas características clínicas, tratamento medicamento e conhecimento da farmacogenética dos medicamentos é de grande importância para controle adequado da doença e melhora da qualidade de vida.

PALAVRAS-CHAVE: Transtorno do espectro autista. Risperidona. Aripiprazol.

Central Message

ASD is a neurodevelopmental disorder characterized by behavioral signs accompanied by persistent deficits in communication and social interaction, repetitive and stereotyped behavior patterns, and a restricted repertoire of interests. Its diagnostic characteristics classify it into 3 levels, I, II and III, according to the severity and level of support required. Currently, the treatment of severe behavioral symptoms related to ASD is carried out with antipsychotics, especially with risperidone and aripiprazole

Perspective

It was observed that ASD manifests itself in a diversified way, and the understanding of its clinical characteristics, drug treatment and knowledge of applied pharmacogenetics is of great importance for adequate disease control and improvement of patients' quality of life. A better understanding of the influence of CYP2D6 enzyme genetic polymorphisms on treatment with risperidone and aripiprazole in children and adolescents is necessary to evaluate their relationship with pharmacogenomics and the improvement of the clinical picture presented by patients.

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INTRODUCTION

Historically, the term autism was coined by Swiss psychiatrist Eugen Bleuler in 1908. In 1943, another psychiatrist, Leo Kanner, made a diagnostic categorization with characteristics and complications that delimit the clinical picture for autism.[1]

In 2013, the nomenclature currently used "Autism Spectrum Disorder" (ASD) emerged after changes resulting from years of revision by the Neurodevelopmental Disorders Committee created specifically for this purpose, which originated the DSM-5 (Diagnostic and Statistical Manual of Mental Disorders) and defined the ASD criteria currently used.[2] In addition, the subdivisions formerly known as "Classic Autism, Atypical or Not Otherwise Specified Autism, and Asperger's Syndrome" were grouped into a single group known as the autism spectrum.[2,3]

The U.S. Food and Drug Administration (FDA) recommends the use of second-generation antipsychotics, such as risperidone and aripiprazole, for the treatment of behavioral symptoms of ASD in children and adolescents, including aggression, irritability, and disruptive behaviors.[4] Although these drugs demonstrate efficacy in controlling symptoms, in many cases significant variability in therapeutic response and incidence of adverse effects is observed, limiting their benefit in a considerable part of patients.[5]

One of the main factors influencing this variability is the genetic diversity in the cytochrome P450 enzyme CYP2D6.[6] This enzyme plays an important role in the metabolism of both risperidone and aripiprazole, regulating their plasma concentrations and, consequently, their efficacy and safety profile.[6] Thus, genetic polymorphisms in CYP2D6 can lead to marked differences in the way each individual responds to treatment, requiring individual strategies to optimize clinical outcomes.[7]

The aim of this review was to describe the influence of genetic polymorphisms of the CYP2D6 enzyme on treatment with risperidone and aripiprazole in children and adolescents with ASD, evaluating their relationship with pharmacogenomics.

METHOD

An electronic search was performed from January 2023 to December 2023 in the main databases, including PubMed/MEDLINE, SciELO, LILACS, EMBASE, and Cochrane Library, using combinations of MeSH/DeCS descriptors and free terms related to ASD, drugs ("risperidone", "aripiprazole"), clinical manifestations ("disruptive behavior", "irritability", "stereotypies"), and pharmacogenomics ("CYP2D6*3 and CYP2D6*4 alleles"), "metabolizers"). Articles in Portuguese, English, and Spanish, published between 2010 and 2024, were included. The inclusion criteria established were: studies describing the clinical manifestations of ASD in children and adolescents; to evaluate the use of risperidone or aripiprazole in the treatment of these manifestations; gene variants and CYP2D6 polymorphisms; randomized controlled trials, observational studies, or systematic reviews; and full-text articles available. Isolated cases, anecdotal reports, and publications without a clearly described methodology were excluded.

The article selection process took place in 3 stages: 1) initial screening by title and abstract; 2) full reading of the pre-selected articles; and 3) extraction of the relevant data. Two independent reviewers conducted this process, with a third reviewer being consulted in case of disagreement.

Thus, in the end, 72 articles were included

DISCUSSION

Characteristics of ASD

According to the DSM-5, it is a neurodevelopmental disorder characterized by behavioral signs accompanied by persistent deficits in communication and social interaction, repetitive and stereotyped behavior patterns, and a restricted repertoire of interests. Its diagnostic characteristics classify it into 3 levels, I, II and III, according to the severity and level of support required.[2,8,9]

At level I, there is notable social impairment in the absence of support and difficulties in initiating interactions, sometimes they seem to have reduced interest in them, with unsuccessful attempts at social contact, in addition to difficulty in organizing, planning and a certain inflexibility of behaviors.[8,10] Level II requires substantial support with apparent social impairments, limitations in initiating and maintaining interactions, inflexibility in behavior, and difficulty in dealing with change.[8,10] Level III requires a lot of substantial support, with severe deficits in social communication skills, inflexibility of behavior, and extreme difficulty with change. Thus, the lower the degree of impairment of the level, the better the prognosis tends to be.[8-10]

A striking and consistent characteristic of ASD is that it is diagnosed more frequently in males. According to the DSM-5 and statistics from the CDC (Centers for Disease Control and Prevention), ASD is 4 times more frequent in men than in women.[2,11]

Loomes, Hull and Mandy[12], showed that girls with ASD face a higher risk than boys of having their diagnosis neglected or made late, possibly due to the female ASD phenotype, which differs subtly from conventional conceptualizations of the disorder. In addition, girls with ASD are less likely to exhibit obvious restricted interests, making it difficult to identify. In addition, the authors demonstrated emerging evidence that girls are more likely to mask their difficulties, making early and accurate diagnosis more challenging. The persistence of female stereotypes among professionals and contact with these individuals, such as teachers, pediatricians, psychiatrists, and psychologists, may contribute to this diagnostic bias, reducing their sensitivity to symptoms when they occur in girls.[11,12]

Diagnosis of ASD

CDC stipulates that the steps in the process of diagnosing ASD begin with follow-up and surveillance, which consists of monitoring development, seeking its milestones in all children through tools with validity to

identify if they are acquiring basic skills that can help determine possible delay. Then, perform comprehensive developmental assessment by thorough review of how the child plays, learns, communicates, acts, and moves, and how these traits are over time. This evaluation may include clinical observation, parental reports on development and health history, psychological testing, and speech and language assessments. To rule out other disorders, neurological and genetic testing can be used.[11]

There are also other screening tests, including: 1) the Autism Classification Scale in Childhood; 2) Clinical Risk Indicators for Child Development, and 3) the Modified List for Autism in Children.[8]

The diagnosis of ASD is defined as being early, when it is made before the age of 6 and late, after the age of 6. It is important to note that the sooner the child is diagnosed, the sooner they can access services and support, providing better adaptation for the individual and their family.[11,13]

Prevalence of ASD

WHO (World Health Organization) estimates that autism affects 1:100 children in the world.[14] In the United States, data from the CDC show that there are approximately 1:36 children at the age of 8 years with ASD.[11]

In the last 30 years, there has been a 20-fold increase in its prevalence, reaching an annual rate of more than 2% of autistic people in the United States alone.[15] The reason for the increase in incidence in the last 20 years has not yet been clarified. King et al.[16] and Schieve et al.[17] analyzed the effect of changes in the age of the parents and certain perinatal risk factors on the prevalence of ASD, under the hypothesis of a causal pathway, concluding that the contribution of these factors to the increase in ASD incidence is probably minimal. On the other hand, the studies by Parner et al.[18] and King and Bearman19, by focusing on non-etiological factors, concluded that the earlier age at the time of diagnosis and the expanded access to diagnostic methods are some of the factors responsible for the increasing prevalence of ASD.

Etiology of ASD

Currently, it is considered a disease of complex interaction between genes and environment, that is, of multifactorial inheritance, with a genetic component that varies between 40-80%.[20,21]

The involvement of chromosomal regions and variants in specific genes were associated with increased risk for their development.[22] Among the main causes, copy number variants (CNVs), cytogenetically observable chromosomal abnormalities, and monogenic disorders can be mentioned.[23,24] However, it is unclear whether the involvement required to result in the ASD phenotype is single-gene in combination with non-genetic factors, multiple genes through locus heterogeneity, or allelic. The association of multiple genes in combination with non-genetic factors is also suggested.[25]

More than 800 genes have already been related to the disorder, and some of those reported with strong association are: DRD4, SCN2A, CHD8, GRIN2B, DMPK, FXN, CA2, DDHD1, NSUN2, PAH, NLGN3, SHANK3, RARB, ROGDI, SLC1A1, USH2A, CHD2, HDAC4, GDI1. 26-29 In addition, many ASD-related genes are located on the X chromosome, and are involved in chromatin remodeling, synaptic function, neuronal signaling, and brain neurodevelopment.[30]

There are also reports of the presence of chromosomal microdeletions or duplications in children with ASD in chromosomal regions 1q24.2, 1p36.22, 2p13.1, 2q13, 2q37.3, 3p26.2, 4q34.2, 6q27, 6q24.3, 7q35, 8q24.22, 9p21.3, 9q31.2, 12p13.31, 13q13.2-q22, 15q11-q13, 15q11.2, 15q22, 16p11.2, 16p13.2, 17p11.2, 18q21.1, Xp2 and 22q11.[31-34]

Just as genetic variations are related to the etiology of the disorder, the body's response to a given pharmacological treatment is also influenced by the genetic profile.[35]

Treatment of ASD

The heterogeneity of ASD is extremely important to define the types of interventions needed; after all, its wide phenotypic variability directly reflects on different responses to the treatments established as standard.[36] The use of naturalistic behavioral approaches of early onset is recommended; however, there are controversies that show different levels of effectiveness for each modality of therapy. Likewise, no medication is effective in isolation for the treatment of ASD, and it is recommended to individualize drug treatment and interventions according to the target behaviors to be worked on.[36]

Therapeutic interventions, including behavioral strategies and habilitative therapies, are the cornerstones of ASD management and address communication, social, daily living, play, and leisure skills, and maladaptive or maladaptive behaviors.[37]

Pharmacological treatment is prescribed for certain patients, aiming to alleviate some specific symptoms, and not the disorder itself, such as aggressiveness, irritability, significant sleep changes, self-injurious behavior, repetitive behaviors (e.g., perseverance, obsessions, compulsions, and stereotyped movements), mood lability, anxiety, hyperactivity, lack of attention, destructive behavior, or other disruptive behaviors.[38,39]

Recent research indicates that approximately 45% of children and adolescents and up to 75% of adults with ASD are treated with antipsychotic medication. They are drugs with psychotropic action, which inhibit psychomotor function by acting on the nerve cells that regulate psychic processes.[40]

Atypical antipsychotics

Atypical antipsychotics (AAPs), or second-generation antipsychotics, are called "atypical" because they are considered safer and better tolerated than "conventional" or first-generation antipsychotics, including risperidone and aripiprazole.[41]

These medications are widely used in the other generalized developmental disorders (PDDs) to treat maladaptive behaviors. PACs are available in several forms of application, and the main use in ASD is the oral route.[41]

These AAPs are all potent antagonists of dopamine D2 receptors and, also, have additional properties, as they are antagonists of 5-HT2A and 5-HT1A receptors, belonging to the serotonin receptor family, inhibiting the reuptake of serotonin and/or norepinephrine.[42]

AAPs with action of D2 receptor antagonists combined with 5-HT2A receptor antagonism have greater efficacy for symptoms of mania and depression. Antipsychotics also exhibit histamine, muscarinic (cholinergic), and alpha-adrenergic antagonism.[43]

Risperidone

Since 2006, the FDA has approved risperidone to treat ASD-related irritability.[4] Approximately 1 in 9 young people with ASD use this medication.[2,44]

Its effect on aggression, stereotypies, irritability, and restlessness is attributed to dopamine antagonism, while its effect on restricted activity patterns, communication, social, and emotional skills, such as difficulty maintaining eye contact and attention, is attributed to serotonin antagonism.[4] This drug also blocks alpha-1 adrenergic receptors and, to a lesser extent, histamine H1 and alpha-2 adrenergic receptors.[5]

The major route of metabolization of risperidone is in the liver, where it undergoes hydroxylation producing 9-hydroxyrisperidone, or paliperidone, as its active metabolite, this reaction is catalyzed primarily by the enzyme CYP2D6, and to a lesser extent by CYP3A4 and CYP3A5.[45]

Although there are no mandatory requirements for monitoring of therapeutic drugs (TDM) with risperidone, monitoring of plasma concentrations of this drug is strongly recommended by European guidelines. Therapeutic monitoring can help assess compliance and identify drug concentrations, which may be low, resulting in therapeutic failure.[46] In addition, monitoring the level of the drug can help in the evaluation of potential drug interactions and side effects.[46]

Safety, efficacy, acceptability, and tolerability have been evaluated in several clinical studies for the treatment of ASD symptoms. According to Hutchinson et al.[47,] and Mano-Souza et al.[4,] risperidone has demonstrated a response rate of 70% in efficacy for the treatment of maladaptive symptoms of ASD, both short-term (up to 8 weeks) and long-term (after 8 weeks) use.

On the other hand, Maneeton et al.[48,] showed that the acceptability, defined as the overall discontinuation rate, of risperidone treatment was comparable to placebo, and no difference in treatment was found between risperidone and placebo for tolerability.

In another study, Mano-Souza et al.[4,] on the use of risperidone, both in the short and long term in children with ASD showed general improvement in maladaptive behaviors.

Aripiprazole

Aripiprazole is an FDA-approved atypical antipsychotic used for the management and treatment of schizophrenia, mania associated with bipolar disorder, irritability associated with ASD, major depressive disorder, and Tourette's syndrome.[49] He is a partial agonist of dopamine D2 and serotonin 5HT-1a receptors and an antagonist of the serotonin 5HT-2a receptor. It has a high affinity for D2, D3, 5HT-1a, and 5HT2a receptors and moderate affinity for D4, 5HT-2c, 5-HT7, alpha-1 adrenergics, and H1 receptors. This drug demonstrates functional selectivity in intracellular signaling pathways, requiring an occupancy rate greater than 90% in D2 receptors to be clinically active, thus not producing so many extrapyramidal symptoms.[50]

The half-life of oral administration is approximately 75 h. Constant serum concentration doses (based on 15-30 mg per day) should occur in approximately 14 days and therefore it may take up to 2 weeks to fully assess tolerability.[49]

Aripiprazole metabolism occurs by hepatic dehydrogenation, hydroxylation, and N-dealkylation via CYP2D6 and CYP3A4, genes of the CYP450 family.[51] Taking this medication require monitoring for any side effects, and antipsychotic switching should be considered if weight gain is greater than or equal to 5% of initial weight.[49]

The main route used in ASD is oral and its dosage is available in tablets of 2 mg, 5 mg, 10 mg, 15 mg, 20 mg and 30 mg.[49] The study by Hirsch and Pringsheim52 demonstrated that the short-term use of aripiprazole in ASD resulted in a decrease in irritability, hyperactivity, and stereotypies.

Adverse effects of antipsychotics

PAOs can cause adverse effects such as weight gain, hyperlipidemia, diabetes mellitus, prolongation of the QTc interval on the electrocardiogram, extrapyramidal symptoms, myocarditis, agranulocytosis, cataracts, and sexual side effects.[53] Treatment with these drugs can contribute to weight gain and, subsequently, to metabolic syndrome with hyperglycemia, hypertension, hyperlipidemia, and hypertriglyceridemia, which are risk factors for stroke, myocardial disease, and diabetes mellitus.[53]

Weight gain, metabolic changes, and sleepiness are significant concerns when using risperidone. This drug may also produce extrapyramidal symptoms (EPS), including acute dystonia, akathisia, tardive dyskinesia, and parkinsonian symptoms.[54,55]

Regarding aripiprazole, although its side effects are similar to those found in typical and atypical antipsychotics, the degree of EPS and metabolic syndrome are lower due to the specificity of its receptor.[49] Aripiprazole is associated with lower incidences of weight gain, hypercholesterolemia, hyperglycemia, and cardiovascular abnormalities. Other possible side effects include drowsiness, nausea, vomiting, akathisia, and dizziness. Rare adverse effects may include neuroleptic malignant syndrome, liver function abnormalities and jaundice, seizures, and agranulocytosis.[49,56]

Pharmacogenomics

Pharmacogenomics is the science that studies the interaction between genes and drugs.[57] From the analysis of specific regions of DNA, it is possible to verify genetic markers such as single-nucleotide polymorphisms (SPN),

microsatellite insertions, deletions and repeats, and RNA splicing.[57,58] The main targets of pharmacogenomics are the genes that encode enzymes responsible for the pharmacokinetics (events of absorption, distribution, metabolism, and excretion of the substance at its systematic concentration) and pharmacodynamics (relationship between the administered dose and the effects produced) of licit and illicit drugs.[57,58]

CYP2D6

The cytochrome P450 (CYP) superclass is a family of enzymes found in several species and are named for their ability to absorb light at a frequency of 450 nm.[6,59]

The human genome contains 57 CYP genes, of which 12 of the enzymes produced are associated with the metabolism of about 80% of the drugs most commonly used by the population.[60] The CYP2D6 gene is located at 22q13.[1] and is composed of 9 exons, with 1491 base pairs encoding 497 amino acids and 8 introns.[61]

CYP2D6 is responsible for metabolizing approximately 25% of drugs by encoding monooxygenase proteins, which participate in phase I metabolism.[61,62] These enzymes metabolize drugs such as antivirals, opioids, beta-blockers, antidepressants, antipsychotics, antiarrhythmics, antihistamines, and β blockers, among others.[61,63]

Deficiency of CYP2D6 activity is inherited as an autosomal recessive trait and its genetic variants may be CNVs or SNPs.[7] Are natural variations found in genes and CYP2D6 and can have significant influence on metabolism, clinical efficacy, and side effects in drug therapy, depending on whether it modifies the amino acid sequence of the encoded protein and whether it has physiological consequences.[64] If several SNPs occur in the same gene, the resulting genotypes can form haplotypes, which would be when different genetic variants segregate together in the formation of gametes, which would characterize linkage imbalance. There are many functional patterns of CYP family polymorphism that result in mutations such as nucleotide substitution, change in reading matrix, splicing defects, insertion/deletion, tandem rearrangement, gene deletion, and duplication.[65]

This significant alteration of polymorphisms in the CYP2D6 gene alters the pharmacokinetics and pharmacodynamics of drugs such as risperidone and aripiprazole, which may lead to the occurrence of toxic effects and therapeutic failure, which could explain why drug therapy is ineffective in some individuals.[65]

According to the Human Cytochrome P450 Allele Nomenclature Committee (CYP), from 2010, the CYP2D6 gene is highly polymorphic, with more than 90 allelic variants, which can significantly affect enzymatic activity, generating 4 different phenotypes of metabolizers: 1) non-functional isoforms (weak); 2) isoforms with reduced function (intermediate); 3) functional isoforms (normal) and 4) isoforms with increased function (ultra-fast).[65]

Genetically, individuals who have 2 normal alleles or one normal and one altered are classified as normal metabolizers (NMs).[65] Individuals with 2 inactive copies of the CYP2D6 gene are called slow metabolizers (PMs) and have slow breakdown of medications, that is, they have decreased metabolization capacity, making side effects more exacerbated and the standard dose of certain drugs may not work as expected and up to 15% of the population fits into this subgroup.[66] Intermediate metabolizers (MIs) may somehow have the metabolism of drugs altered, causing effects similar to PMs, but not as pronounced.[65] Ultrafast (UMs) metabolize drugs very quickly, because they have alleles that produce enzymes with high activity or have extra copies of alleles (e.g., gene duplications or triplications).[58]

Globally, NMs and IMs phenotypes are the most common, comprising 43-67% of populations.[67] PMs and UMs are less common, but these individuals are at higher risk for adverse reactions or treatment failure when treated with a drug that is metabolized or bioactivated by CYP2D6.[67]

Lopes et al.[68] reported that the CYP2D6*3 variant exerts an influence on opioid metabolization. Regarding the importance of the CYP2D6*4 variant, Scantamburlo et al.[69] showed that this allele leads to the change in the reading matrix at position 259 of the protein, generating an enzyme with little or no metabolizing function.

The CYP2D6*3 and CYP2D6*4 alleles are the most important null variants of the protein, responsible for the absence of enzymatic activity, thus causing poor metabolism.[70] These alleles are the most prevalent of Eurodescendants, *3 appears in 1.6% and *4 in 18.5% of this population.[67]

The alleles of CYP2D6*1, CYP2D6*2, CYP2D6*33, and CYP2D6*35 are normal; while CYP2D6*3, CYP2D6*4, CYP2D6*5, and CYP2D6*6 express isoenzymes with no activity, and CYP2D6*10, CYP2D6*17, CYP2D6*29, and CYP2D6*41 encode enzymes with reduced activity.[71,72] The CYP2D6*1 allele is considered the reference allele and is often inferred when no variant is detected by genotyping test.[70]

CONCLUSION

From this review, it is concluded that autism spectrum disorder manifests itself in a diversified way, and the understanding of its clinical characteristics, drug treatment and knowledge of pharmacogenetics applied to these drugs is of paramount importance for adequate disease control and improvement of patients' quality of life.

Authors' contributions
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