DOWN SYNDROME AS A GENETIC RISK FACTOR FOR ALZHEIMER'S DISEASE: AN INTEGRATIVE REVIEW OF MOLECULAR MECHANISMS

SÍNDROME DE DOWN COMO FATOR DE RISCO GENÉTICO PARA A DOENÇA DE ALZHEIMER: UMA REVISÃO INTEGRATIVA DOS MECANISMOS MOLECULARES

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ABSTRACT

Objectives: To explain why Down syndrome (DS) is considered a risk factor for Alzheimer's disease (AD) by describing the genetic markers involved in this relationship.

Methodology: The following descriptors were used in the Virtual Health Library and PubMed databases in English and Portuguese: "Down syndrome", "trisomy 21", "Alzheimer's disease", "dementia", "mongolism", "aging", "Alzheimer's dementia", "risk factors", and "genetics". Of the 45 studies found in the PubMed database, 15 were selected for review.

Results: The enhanced life expectancy of individuals with DS has been increasing the risk for AD incidence in this population. This progression, the genetic risk factors from trisomy 21 (especially the complete form), and extra copies of genes (e.g., amyloid-β precursor protein) increase the risk for developing AD by triggering events, such as excess production of the amyloid-β peptide.

Conclusion: Trisomy 21 and its genetic and molecular effects are the main factors for the onset of AD, showing the need for further studies to elucidate the genetic relationship between AD and DS.

Keywords: Down syndrome, Alzheimer's disease, risk factors, genes.

RESUMO

Objetivos: Explicar os motivos da síndrome de Down ser considerada um fator de risco para a doença de Alzheimer, por meio da descrição dos marcadores genéticos envolvidos nessa relação.

Metodologia: Foram feitas buscas na Biblioteca Virtual em Saúde e na PubMed, com uso destes descritores, em inglês e português: "síndrome de Down", "trissomia do 21", "doença de Alzheimer", "demência", "mongolismo", "envelhecimento", "demência por Alzheimer", "fatores de risco" e "genética". Dentre os 45 artigos recuperados, 15 foram selecionados, todos referentes à PubMed.

Resultados: O aumento da expectativa de vida das pessoas com síndrome de Down trouxe uma maior probabilidade para a incidência da doença de Alzheimer nesses indivíduos. Essa evolução se juntou aos fatores de risco genéticos advindos da trissomia, em especial da sua forma total, e às cópias extras de genes, a exemplo do gene da proteína precursora β-amiloide, elevando ainda mais a probabilidade de desenvolvimento dessa doença, por desencadear eventos como o excesso do peptídeo β-amiloide.

Conclusão: A trissomia do cromossomo 21 e os seus efeitos genéticos e moleculares são agentes basilares no amplo surgimento da demência pela doença de Alzheimer, comprovando-se a necessidade de mais estudos que elucidem a relação genética entre essa patologia e a síndrome de Down.

Palavras-chave: Síndrome de Down, Doença de Alzheimer, Fatores de risco, Genes.

INTRODUCTION

Down syndrome (DS) is the most common condition among intellectual disabilities, affecting between 5 and 8 million people worldwide[1]. The advances in multidisciplinary care related to DS increased the life expectancy of these individuals and the risk for dementia due to Alzheimer's disease (AD), which has an 80% prevalence in individuals with DS aged over 65 years[2].

In this context, DS is considered the main genetic risk factor for early-onset AD. Also, AD is the leading cause of dementia, characterized by short-term memory loss and subsequent loss of other cognitive abilities due to reduced neuronal activity[3].

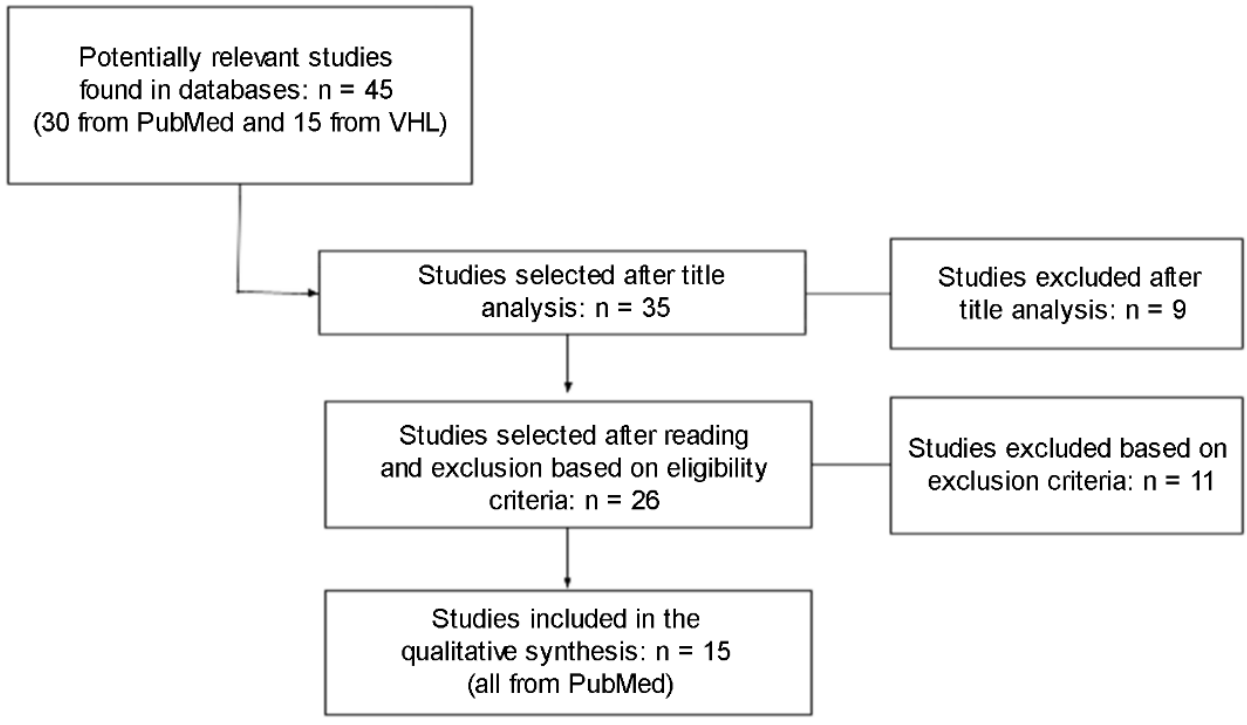
According to the 2013 Guidelines for Care of People with Down Syndrome[4], among the genetic causes of an extra chromosome 21, 95% occur due to simple trisomy, 3% to 4% due to Robertsonian translocations, and 1% to 2% due to mosaicism. This etiological variety contributes to the diverse phenotypic presentations of DS.

Despite the phenotypic variability, the primary cause of mortality in individuals with DS is AD and its complications5 since this neuropathology is caused by an activation of several genes located on chromosome 21, which are triplicated in DS. For example, the amyloid-β precursor protein (APP) is cleaved into amyloid-β (Aβ) peptide when its gene is excessively produced, accumulating and forming amyloid plaques responsible for the pathogenesis of AD[6]. However, several other genes also participate in the onset of AD7, such as superoxide dismutase type 1 (SOD1) and dual-specificity tyrosine-phosphorylation-regulated kinase 1A (DYRK1A)[8]. Also, AD was described in all adults with DS aged around 40 years, evidencing the relationship between AD and DS[5].

DS is considered the main genetic risk factor for AD due to their physiological similarities. Consequently, the advancing age of adults with DS (especially between 60 and 69 years) increased the number of AD diagnoses, estimated as 54.5% of cases in this age group[9]. Both diseases have a noticeable genetic relationship, highlighting the need for more studies on their similarities. Therefore, this review aimed to explain why DS is considered a risk factor for AD and the importance of data on this topic to prove their shared molecular aspects.

METHODS

Figure 1. Flowchart of study selection for the integrative review.



VHL: Virtual Health Library.

This integrative literature review was conducted based on a compilation of primary sources using the Virtual Health Library and PubMed databases. The following descriptors and their variations in Portuguese and English were used for the searches: “Down syndrome”, “trisomy 21”, “Alzheimer’s disease”, “dementia”, “mongolism”, “aging”, “Alzheimer’s dementia”, “risk factors”, and “genetics”.

The following inclusion criteria were used for screening: (a) studies in English and Portuguese; (b) DS and AD as central topics; (c) genes affected by trisomy 21 and related to AD; and (d) epidemiological data on dementia in individuals with DS. Studies not meeting the inclusion criteria (a) and (b), lacking information on the genetic aspects of DS and its influence on AD, without pathophysiological markers for AD, or published more than nine years ago were excluded. After the search, 45 studies were found; 15 were selected from the PubMed database.

RESULTS AND DISCUSSION

Chart 1. Integrative chart with the selected studies.

DOWN SYNDROME AS A GENETIC RISK FACTOR FOR ALZHEIMER'S DISEASE: AN INTEGRATIVE REVIEW OF MOLECULAR MECHANISMS					
No.	Title	Author/Year	Objective	Results	Conclusion
01.	"Down's syndrome, neuroinflammation, and Alzheimer neuropathogenesis"	WILCOCK D., GRIFFIN W., 2013.	To explain the neuroinflammatory responses in the brains of individuals with DS during fetal development and their relation to EOAD.	The APP of Aβ plaques is the main genetic factor linking DS to AD, and its gene is located on chromosome 21. Also, glial cells increase, resulting in the overexpression of a product from chromosomes 2 (interleukin-1) and 21 (S100B). Thus, cytokines may regulate the EOAD in individuals with DS.	Many genes positively regulate the immune responses of microglial cells, while others promote the overexpression of pro-inflammatory proteins.
02.	"Down syndrome and Alzheimer disease: common pathways, common goals"	HARTLEY D. et al., 2015.	To explain the common pathogenic mechanisms between DS and AD and the goals for diagnosing and treating AD in individuals with DS.	Most adults will develop AD around the age of 40 years, which is mainly characterized by early deposition of Aβ peptides in extracellular plaques and brain vessel walls. Later, neurofibrillary tangles accumulate, especially in the hippocampus, entorhinal cortex, and neocortex.	The care for individuals with DS has been improving along with their life expectancy. However, this improvement increased the risk for AD since most genes associated with AD pathogenesis are located on chromosome 21. Therefore, individuals with DS should be included in AD biobanks, and clinical trials involving this population might provide valuable insights.
03.	"A genetic cause of Alzheimer disease: mechanistic insights from Down syndrome"	WISEMAN F. et al., 2015	To present an overview of the clinical and pathological characteristics of AD in individuals with DS compared with other forms of AD to highlight shared genetic, pathogenic, and protective mechanisms and discuss future research topics.	DS is associated with a high risk for EOAD, mainly justified by the presence of three copies of the APP gene. The APP leads to an accumulation of Aβ in the brain when excessively cleaved. Also, the distribution and biochemical composition of Aβ plaques and neurofibrillary tangles in individuals with DS, EOAD, or LOAD are similar. A rare form of familial EOAD can also be observed, which is caused by the duplication of the APP trait from small internal duplications of chromosome 21, leading to three copies of the APP gene.*	Many questions still need to be answered regarding the relationship between DS and AD, especially mechanisms responsible for the late onset of dementia compared to duplication of APP, how changes in neurodevelopment affect neurodegeneration, and the possible gene(s) on chromosome 21 that protect against dementia.

04.	"Is apolipoprotein E4 an important risk factor for dementia in persons with Down syndrome?"	ROHN. T. T. et al., 2015.	To assess the potential risk and frequency of the APOE4 allele in individuals with DS through a literature review.	Three of the studies concluded that carrying the APOE4 allele did not increase the risk of developing AD dementia in individuals with DS. One of these studies included young individuals with DS, which may have biased the results toward a null effect. Of the ten studies, six showed a potential risk for AD dementia or increased mortality in individuals with DS with APOE4, and Deb et al. documented a tendency of risk for AD (not statistically significant). Two studies (Deb et al. and Coppus et al.) also conducted a meta-analysis of all previously published similar studies. Zigman et al. found that individuals with DS without dementia who had at least one APOE4 allele were approximately five-fold more likely to die than those with APOE3 allele. Prasher et al. showed a risk ratio of 5.9 in individuals with DS without dementia who had at least one APOE4 allele compared with a risk ratio of 1.0 for the APOE3/3 group. Thus, the APOE4 allele may lead to early mortality in individuals with DS, independent of dementia risk.	DS has a complex etiology and is considered a model for EOAD due to the triplication of the APP gene on chromosome 21. Thus, adults with DS above 40 years old have neuropathological criteria (including senile plaques) consistent with AD and are more likely to develop dementia than the general population. Considering the similarities between these two conditions, risk factors for AD may also increase the risk for dementia in DS. Also, the APOE4 allele represents the most critical genetic factor for LOAD, with 65% to 80% of all individuals with AD carrying at least one allele. However, results on whether the APOE4 gene has the same potential risk for dementia in DS are conflicting. The presence of the APOE4 allele may increase the risk of dementia in individuals with DS despite the lower risk than for AD. Several studies supported an increased risk for mortality in individuals with DS with the APOE4 allele, independent of dementia risk.

05.	"Telomere longitudinal shortening as a biomarker for dementia status of adults with Down syndrome"	JENKINS E. C. et al., 2015	To verify whether the progression of cognitive and functional declines due to AD reduces the telomere. Sequential changes in telomere length were examined in five individuals with DS (three women and two men) during the transition from preclinical AD to MCI-DS (N ¼ 4) or dementia (N ¼ 1).	Consistent telomere shortening was observed over time. Telomere lengths before clinical decline were similar to those of adults with DS who did not experience clinical decline. However, telomere lengths after the transition to MCI-DS or dementia were similar to those of adults with DS who developed MCI-DS or dementia.	The rapid conversion to clinical practice may improve diagnostic accuracy for individuals with DS developing AD, contributing to better planning to support needs. Negative results in individuals with symptoms mimicking dementia may encourage the search for the cause of these symptoms and effective treatment.
06.	"Down syndrome, increased risk of dementia and lipid disturbances"	KLOSOWSKA A. et al., 2017.	To highlight the importance of understanding the early development of dementia, obesity, and metabolic disorders in individuals with DS, which may lead to brain tissue degeneration, cerebrovascular disorders, and a significant impact on the quality of life of these individuals and their families.	Over 70% of individuals with DS up to 55 to 60 years old showed early signs of dementia consistent with those of AD. These signs were primarily due to the complete or partial triplication of various genes on chromosome 21 (e.g., APP, SOD1, CBS, DYRK1A, and SYNJ1). These genes influence the cascade of Aβ peptide production, which is negatively correlated with HDL. Also, HDL suppresses Aβ peptide production by reducing cellular cholesterol through activated cholesterol efflux mediated by ABC transporters. *	Although many studies have analyzed lipid and lipoprotein levels in individuals with DS, few related these markers to memory impairment, which could be useful for better understanding the pathological mechanism of dementia.

07.	“Aging with Down syndrome: the dual diagnosis: Alzheimer disease and Down syndrome”	CIPRIANI G. et al., 2018.	To explore the dementia in DS.	Most individuals with DS aged between 35 and 40 years exhibited characteristic neuropathological changes of AD. However, only a small portion of this group developed clinical dementia around the age of 50, and the initial signs may differ compared with the general population. *	Adults with DS had a high risk for AD, and the development of dementia may differ from the observed in the general population. Therefore, failing to recognize it may delay the diagnosis and interventions, affecting cognitive decline, behavioral, and emotional aspects. Many studies have attempted to standardize the assessment of individuals with DS and AD, but a gold standard for diagnosis is still lacking.
08.	“Association of dementia with mortality among adults with Down syndrome older than 35 years”	HITHERSAY R., STARTIN C., STRYDOM A., 2019.	To explore the association of AD dementia with mortality and factors associated with dementia in adults with DS.	Of 211 adults with DS, 96 (45.5%) were women, and 66 (31.3%) had a clinical diagnosis of dementia. The crude mortality rate for individuals with dementia was five-fold higher than for those without dementia. In the latter group, epilepsy onset after 36 years old was associated with mortality. *	Most adults with DS who died had dementia and were affected by some associated factors that were not found in the individuals with DS (e.g., APOE genotype). These findings highlighted the need for clinical trials on treatments to prevent or delay dementia in individuals with DS.

09.	“Dementia in Down syndrome: unique insights for Alzheimer disease research”	LOTT I., HEAD E., 2019.	To assess the similarities and differences between the pathological cascades underlying DS and AD, providing a platform for the common exploration of these two conditions.	Post-mitotic somatic mutations resulting in mosaicism may represent a risk factor for AD in individuals with and without DS, suggesting a common topic that could be investigated in future research. Some individuals developed AD due to the duplication of a small region of chromosome 21, which includes APP (Dual-APP). Pathogenic mechanisms in these individuals may parallel those in individuals with DS and AD. An additional copy of APP was present in Dual-APP and DS with AD, contrasting with conditions where other genes (e.g., PSEN1 or PSEN2) are mutated, and APP processing was changed independently of genetic copy number. Dual-APP shared some common traits with DS, including early onset of dementia (average age of 52 years for Dual-APP), AD, and increased prevalence of cerebral amyloid angiopathy. Individuals with Dual-APP presented no phenotypic characteristics of DS. Although most individuals with DS had AD, variability in dementia prevalence was more pronounced in DS than Dual-APP, whereas cerebral amyloid angiopathy was less prevalent in DS than Dual-APP. These phenotypic differences between DS and Dual-APP provided a platform for better understanding the roles of genes on chromosome 21 (except for APP) in AD pathogenesis.	DS allows the monitoring of temporal events and pathways of important mechanisms for AD throughout life. Research areas include similarities and differences in molecular markers of pathogenesis, targets for therapeutic intervention, predictive studies, evolution of significant clinical biomarkers, and course of APP throughout life and its relation to dementia onset in the brains of individuals with DS. Thus, systematic large-cohort studies should be developed in the population with DS.

10.	"Down syndrome, Alzheimer disease, and cerebral amyloid angiopathy: the complex triangle of brain amyloidosis"	CARMONA--IRAGUI M. et al., 2019.	To review the available evidence on various aspects of cerebrovascular disease in DS, focusing on cerebral amyloid angiopathy and characterization of pathophysiological mechanisms by biomarkers.	The overexpression of the APP gene leads to excessive production and deposition of the Aβ peptide (main marker of AD development) and cerebral amyloid angiopathy. Individuals with DS develop neuropathological characteristics of AD by the age of 40 years, with an increased risk for cognitive impairment related to this neuropathology. The walls of leptomeningeal and cortical vessels become fragile and prone to bleeding due to progressive deposition of the Aβ peptide, defining cerebral amyloid angiopathy. *	General cerebrovascular diseases, especially cerebral amyloid angiopathy, are common in AD. AD and cerebral amyloid angiopathy are considered part of the continuum of cerebrovascular amyloidosis and are associated with DS through pathophysiological mechanisms related to amyloid. DS provides a unique opportunity to study cerebrovascular diseases in a population with a low frequency of conventional vascular risk factors. The limited evidence supported that cerebral amyloid angiopathy is the primary form of cerebrovascular disease in DS.
11.	"Signaling pathways implicated in Alzheimer's disease neurodegeneration in individuals with and without Down syndrome"	MARTÍNEZ-CUÉ C., RUEDA N., 2020.	To provide an overview of the most relevant pathways implicated in the onset and progression of AD in individuals with and without DS.	The complex scenario of AD etiopathology suggested that the development of therapies to treat this disorder should target molecular pathways involved in multiple changed events. DS can be considered a useful model for studying AD etiopathology and pursuing new therapeutic strategies due to the high prevalence and EOAD in this population and the multiple common mechanisms found in both conditions.	The complex scenario of AD etiopathology suggested that the development of therapies to treat this disorder should target molecular pathways involved in multiple changed events. DS can be considered a useful model for studying AD etiopathology and pursuing new therapeutic strategies due to the high prevalence and EOAD in this population and the multiple common mechanisms found in both conditions.

12.	“Clinical and biomarker changes of Alzheimer disease in adults with Down syndrome: a cross-sectional study”	FORTEA J. et al., 2020.	To characterize the natural history of AD in adults with DS.	A total of 388 adults with DS (347 in Barcelona and 41 in Cambridge) and 242 euploid controls (Barcelona) were recruited between February 1st, 2013, and June 28th, 2019 (Barcelona), and June 1st, 2009, and December 31st, 2014 (Cambridge). Most individuals with DS (45%) and euploid controls (67%) were female. Trisomy of chromosome 21 was present in 308 individuals with DS; 80 individuals had no genetic confirmation. A total of 72 (19%) individuals with DS had mild, 175 (45%) had moderate, and 98 (25%) had severe or profound intellectual disability. The number of adults with DS and controls differed for each biomarker method.	Individuals with DS were suitable for clinical trials of AD. Describing the natural history of AD in this population would have an immediate effect on the design of such trials.
13.	“Down syndrome and Alzheimer disease: common molecular traits beyond the amyloid precursor protein”	GOMEZ W. et al., 2020.	To highlight recent data on the origin of shared factors between DS and AD and explore the mechanisms related to cognitive impairments in DS associated with dementia.	Changes in chromosome location due to the extra chromosome 21 and epigenetic modifications may promote changes in gene expression beyond this chromosome. Similar pathological features and cellular dysfunctions in DS and AD, including impaired autophagy, lysosomal activity, and mitochondrial dysfunction, may be regulated beyond the APP overexpression.	This review highlighted recent findings on the common molecular pathways between DS and AD, emphasizing less studied aspects (e.g., mitochondrial function and epigenetic regulation).

14.	"Common genetic signatures of Alzheimer's disease in Down syndrome"	SHARMA A. et al., 2020.	To investigate the relationship between AD and DS using integrative analysis of derived genes from peptides associated with amyloid plaques in AD and DS and genes from chromosome 21, risk factors for AD, and differentially expressed genes identified using genome analysis of individuals with DS in the dorsal frontal and cerebellar cortex.	Functional enrichment analysis, characteristics of the transcription factor, and network analyses were used to assess unique and shared aspects of each gene set. Genes identified as important for DS and AD included SOD1, SYNJ1, S100B, ACSM1, APBA2, APLP1, BACE2, BCL2L, COL18A1, DYRK1A, IK, KLK6, METTL2B, mTOR, NFE2L2, NFKB1, PRSS1, QTRT1, RCAN1, RUNX1, and SAP18.	Oxidative stress, apoptosis, and processes of inflammation or the immune system may be the basis for the pathogenesis of DS and AD.
15.	"Alzheimer's disease in Down syndrome: an overview of genetic and molecular aspects"	GOMES F. et al., 2021.	To analyze the biomarkers involved in the neuroinflammation and neurodegeneration processes and understand the mechanisms of AD incidence and EOAD in individuals with DS.	Certain genetic factors in DS, mainly the overexpression of APP, contributed to early-onset dementia and directly influenced the neuroinflammatory response. Also, the development of AD in individuals with DS is complex and involves changes in genes within and outside chromosome 21.	Some genes of chromosome 21 associated with neurological disorders in the context of DS and AD were not analyzed. Therefore, future research may help to map the interaction of genes within and outside chromosome 21 in the neuropathology and neuroinflammation of AD in DS.

Fonte: Autores

AD: Alzheimer's disease; DS: Down syndrome; EOAD: early-onset Alzheimer's disease; LOAD: late-onset Alzheimer's disease; APP: amyloid precursor protein; MCI-DS: mild cognitive impairment related to Down syndrome; APOE4: apolipoprotein E4; Aβ: amyloid-β; SOD1: superoxide dismutase type 1; S100B: S100 calcium-binding protein B; CBS: cystathionine beta-synthase; DYRK1A: dual-specificity tyrosine phosphorylation-regulated kinase type 1A; SYNJ1: synaptojanin 1; HDL: high density lipoprotein; ABC: ATP-binding cassette; PSEN: presenilin; ACSM1: acyl-CoA synthetase medium chain family member 1; APBA2: amyloid beta precursor protein binding family A member 2; APLP1: amyloid beta precursor like protein 1; BACE2: beta-site amyloid precursor protein-cleaving enzyme 2; BCL2L: B-cell lymphoma 2-like protein; COL18A1; collagen type XVII alpha 1 chain; KLK6: kallikrein related peptidase 6; METTL2B: methyltransferase-like protein 2B; mTOR: mammalian target of rapamycin; NFE2L2: nuclear factor erythroid 2-like factor 2; NFKB1: nuclear factor kappa B subunit 1; PRSS1: protease serine 1; QTRT1: queuine tRNA-ribosyltransferase catalytic subunit 1; RCAN1: regulator of calcineurin 1; RUNX1: runt-related transcription factor 1; SAP18: Sin3A associated protein 18.

The advances in care of individuals with DS increased their life expectancy, currently ranging between 55 and 60 years old8. Consequently, the prevalence of this condition also increased, affecting 6 million individuals worldwide[10,11]. However, this increase in lifespan has become one of the main risk factors for developing AD12, classifying this pathology as the leading cause of mortality in individuals with DS[5].

About 88% of individuals with DS will develop dementia by the age of 65 years[13], and most individuals will exhibit neuropathology consistent with AD by the age of 40 years[7]. The trisomy 21 from non-disjunction of chromosomes during maternal meiosis (present in 93% to 95% of individuals with DS)[14] is also a risk factor for developing AD. Also, AD markers appear two or three decades earlier in individuals with DS compared with those without this trisomy[15]. Thus, the early onset causes the preclinical phase of AD, with biomarkers undergoing predictable changes for over 20 years[5].

Trisomy 21 induces extra copies of various genes, such as APP, which encodes the protein of the same name[7]. In contrast to the observed in complete trisomy 21, the APP gene may not have an extra copy when chromosome 21 has partial mutation, resulting in no early-onset AD[10]. The APP is found in the plasma membrane and organelles of the neuron, glial cells, and other peripheral tissues[3]. Also, it is cleaved into soluble amyloid precursor protein alpha (sAPPα) fragments in the non-amyloidogenic pathway by α-secretases enzymes after translation, with a neuroprotective effect. In the amyloidogenic pathway, the APP cleavage occurs through β-secretases (primarily β-secretase type 1 [BACE1])[15] and γ-secretases complex, generating sAPPβ fragments and Aβ peptides, respectively[16]. The Aβ peptide can have 40 or 42 amino acids, and the latter is most likely to aggregate[17]. In this sense, 40-year-old individuals with DS have a disturbance in these enzymes, with reduced α-secretases and increased β-secretases, enabling the production of the Aβ peptide[15].

The increased Aβ peptide from the extra APP gene in individuals with DS is diffusely deposited in greater quantities and can be observed in brain tissues during childhood and adolescence12, triggering immune defense mechanisms (e.g., inflammatory processes)[18]. Over the years, increased aggregation develops neuritic plaques, which are responsible for the neurodegeneration related to AD[19] due to the destruction of neuronal connection, synaptic interruption, tissue loss, and reduced brain mass[18]. A study found that all adults with DS aged 35 to 45 years had neuritic plaques and other changes consistent with AD, affirming that Aβ peptide is one of the main pathophysiological markers of this disease[17].

Although the overexpression of the APP gene is considered the primary precursor to Aβ peptide accumulation[12], other genes are involved in AD development in individuals with DS20. Another finding indicated that the encoding gene of the ETS proto-oncogene 2 contributes to the development of this disease[10]. This gene is in the chromosome 21 and activates the promoter of APP, generating its excessive expression due to trisomy 21 and influencing the formation of Aβ peptides, resulting in diffuse deposits and amyloid plaques[10].

Neurofibrillary tangles are also found due to trisomy [21], tripling their quantity between the fourth and fifth decades of life in individuals with DS[10]. Thus, this is another factor demonstrating the early onset of AD-related dementia in this population[10]. The main genes directly involved in the formation of these markers are those encoding DYRK1A and regulators of calcineurin 1 (RCAN1), found on chromosome 21 and related to hyperphosphorylation of tau protein, which is more abundant in the AD[3].

DYRK1A dysregulates splicing factors, leading to hyperphosphorylation of tau protein by the glycogen synthase kinase 3 (GSK-3) enzyme. The hyperphosphorylation increases tau quantity in the forms with three or four microtubule binding sites (3R-tau and 4R-tau, respectively), contributing to the early onset of neurodegeneration due to neurofibrillary tangles[7]. Also, DYRK1A negatively regulates the quantity of the neuron-restrictive silencer factor protein, which has neuroprotective functions and redu-

ced activity in individuals with DS21.

RCAN 1 stimulates GSK-3 and inhibits the calcineurin enzyme, which dephosphorylates and activates the mitochondrial fission protein, enabling its transport and fission into the mitochondria[3]. Individuals with DS have overexpression of this gene, reducing the efficiency of this mitochondrial process and increasing oxygen consumption, which results in greater oxidative stress[22]. The overexpression of RCAN 1 throughout life triggers harmful cellular effects on synaptic functions, stimulates the formation of neurofibrillary tangles[11], and may inhibit signaling pathways monitored by the nuclear factor of activated T cells, which regulates RCAN 1 expression. Due to these changes in the nuclear factor of activated T cells, the production cascade of Aβ peptides is stimulated primarily by modulation of BACE1 expression, resulting in increased cleavage of the APP[11].

SOD1 is also located on chromosome 21 and involved in oxidative stress. It encodes the superoxide dismutase enzyme, which catalyzes the dismutation of superoxide into molecular oxygen and hydrogen peroxide (a reactive oxygen species). Overexpression of SOD1 in trisomy 21 reduces the activation of catalase and glutathione peroxidase enzymes, which are responsible for converting hydrogen peroxide into water[3]. Consequently, increased levels of hydrogen peroxide induce oxidative stress, inflammatory events, activation of pro-apoptotic factors, and stimulation of cellular senescence, primarily affecting neurons, which become more susceptible to degeneration in individuals with DS[10]. Moreover, this excessive hydrogen peroxide creates a favorable environment for toxicity from Aβ peptides.

The trisomy 21 affects the synaptojanin 1 (SYNJ1) gene, which encodes the lipid phosphatase of the same name, responsible for decreasing levels of phosphatidylinositol-4,5-bisphosphate involved in membrane transduction and their transport during endocytosis in synapses[7]. The mutation causes an increase in the endosome size[23], influencing the pathway of production and accumulation of Aβ peptides in AD in individuals with DS[12]. Corroborating this finding, the reduced expression of SYNJ1 was related to the reduced levels of Aβ peptide, neuronal dysfunction, and cognitive deficits[23].

An additional copy of the cystatin B gene is also observed in trisomy 2110, which encodes the cystatin B enzyme and inhibits the endogenous lysosomal protease that inhibits cathepsins (proteases), causing an imbalance in lysosomal proteolysis. In addition, this change influences the accumulation of Aβ peptides and all their effects in the early-onset AD[3].

Another process contributing to AD in individuals with DS is neuroinflammation, which is mainly related to the triplication of the calcium-binding protein B (S100B) gene on chromosome 21. The S100B gene encodes the S100B cytokine from astrocytes and is involved in the growth and maintenance of neurons. When in excess due to trisomy 21, it is related to prominent growth of dystrophic neuronal processes, especially in amyloid plaques17. In addition, S100B induces mRNA synthesis and translation of APP in neurons[15] and stimulates hyperphosphorylation of tau protein, accumulating the major neuropathological markers of AD10. The S100B also regulates the expression of the interleukin-1 encoding gene (located on chromosome 2), which is involved in the neuropathology of DS and influencing the development of AD[15].

Interleukin-1 is an inflammatory cytokine primarily produced in microglial cells and found in excess due to trisomy 21, leading to the synthesis and evolution of amyloid plaques by inducing the synthesis of the APP in neural cells and other tissues. Also, it stimulates the p38 mitogen-activated protein kinase, an essential enzyme in the hyperphosphorylation of the tau protein and formation of neurofibrillary tangles[15]. Interleukin-1 also reduces synaptophysin and participates in the synthesis and activation of the acetylcholinesterase enzyme that degrades the acetylcholine neurotransmitter, essential for learning and memory abilities, which are early compromised in AD[15]. In addition, the influence of these clinical characteristics induced by interleukin-1 on AD in individuals with DS has been demonstrated and found in more than 70% of

those who exceed the age group of 55 to 60 years[8].

The ubiquitin-specific peptidase 16 (USP16) gene (triplicated in trisomy 21) encodes the specific histone H2 deubiquitinase enzyme related to increased cellular senescence in individuals with DS11. This aging process may also be associated with telomere shortening, in which TTAGGG repeats located at chromosome ends shorten in each cell cycle until the cell is unable to replicate[24]. In this sense, studies have shown a relationship between telomere length in T lymphocytes and development of mild cognitive impairment and dementia in adults with DS[24].

The presence of at least one allele of apolipoprotein E4 (APOE4) in individuals with DS is another genetic factor (not directly influenced by trisomy 21) that contributes to early-onset AD. The inheritance of the APOE4 allele influences the early and rapid increase of endosomes in the preclinical stages of AD and increases the burden of Aβ peptides[25,26]. This mechanism occurs by impairing the clearance of Aβ peptides in brain tissues due to the increased susceptibility of APOE4 to proteolysis. However, further studies should confirm the direct relationship between trisomy 21 and the presence of one or more APOE4 alleles[10,25].

DS is recognized as a genetically determined form of AD, mainly due to the significant increase in the risk of developing AD[5]. These findings emphasized the importance of further studies on the relationship between DS and AD and multidisciplinary care for this population.

CONCLUSION

The DS caused by trisomy 21 (mainly the complete form) influences the early development of AD. This influence arises from the extra copies of genes on chromosome 21 (e.g., APP, ETS proto-oncogene 2, DYRK1A, RCAN1, SOD1, SYNJ1, cystatin B, S100B, interleukin-1 encoding gene, and USP16). Although not located on chromosome 21, the APOE4 is also a significant marker for AD and associated with higher mortality in individuals with DS. Thus, the neuropathological complexity in the relationship between DS and AD requires further studies, focusing on genes triplicated by trisomy 21 and the inheritance of the APOE4 allele. This research field is particularly important due to the increasing life expectancy of individuals with DS, resulting from advances in multidisciplinary care for this population.

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