Down syndrome and associated pathologies: a narrative review of the literature

Síndrome de Down e patologias associadas: uma revisão narrativa da literatura

Síndrome de Down y patologías asociadas: una revisión narrativa de la literatura

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RESUMO

Objetivo: identificar por meio de uma revisão narrativa de literatura as patologias mais recorrentes em indivíduos com Síndrome de Down. **Método:** trata-se de uma revisão narrativa. Realizou-se um levantamento da literatura no Portal Pubmed e nas bases de dados de publicações científicas indexadas: *Scientific Eletronic Library Online* (Scielo), Literatura Latino-Americana e do Caribe em Ciências da Saúde (LILACS), Base de Dados de Enfermagem (BDENF) e *Cumulative Index to Nursing and Allied Health Literature* (CINAHL) e Portal PubMed, usando os descritores "Down's syndrome", "Pathologies", "Trisomy 21", "Intellectual Disability", "Clinical manifestations". **Resultados**: foram encontrados 696 artigos, dos quais 24 foram analisados na íntegra, destes, foram selecionados 9 artigos que compuseram a amostra desta revisão. A maioria dos estudos selecionados mensurou as características fenotípicas peculiares nos indivíduos com essa anomalia, a saber: olhos oblíquos, orelhas baixas, braquidactilia, hipotonia, baixa estatura, braquicefalia, fissuras oblíquas na pálpebra, epicanto, manchas de *Brushfield* na íris, dentre outras. **Conclusão:** torna-se necessária uma atenção e acompanhamento regular dos profissionais de saúde acerca das patologias malignas, doenças autoimunes e inflamatórias que acometem as pessoas com SD.

Descritores: Síndrome de Down; Patologias; Trissomia 21; Deficiência Intelectual; Manifestações Clínicas.

ABSTRACT

Objective: to identify through a narrative literature review the most recurrent pathologies in individuals with Down syndrome. **Method:** this is a narrative review. A survey of literature was conducted on the Pubmed Portal and in the databases of indexed scientific publications: Scientific Electronic Library Online (Scielo), Latin American and Caribbean Literature on Health Sciences (LILACS), Nursing Database (BDENF) and Cumulative Index to Nursing and Allied Health Literature (CINAHL) and PubMed Portal, using the descriptors "Down's syndrome", "Pathologies", "Trisomy 21", "Intellectual Disability" , "Clinical manifestations". **Results:** 696 articles were found, of which 24 were fully analyzed, of which 9 articles were selected that comprised the sample of this review. Most of the selected studies measured the peculiar phenotypic characteristics in individuals with this anomaly, namely: oblique eyes, low ears, brachydactyly, hypotonia, short stature, brachycephaly, oblique clefts in the eyelid, epicant, Brushfield spots on the iris, among others. **Conclusion:** it is necessary to have regular attention and follow-up of health professionals about malignant pathologies, autoimmune and inflammatory diseases that affect people with DS.

Descriptors: Down syndrome; Pathologies; Trisomy 21; Intellectual Disability; Clinical Manifestations.

RESUMEN

Objetivo: identificar a través de una literatura narrativa revisar las patologías más recurrentes en individuos con síndrome de Down. **Método:** esta es una revisión narrativa. Una encuesta de literatura se realizó en el Portal Pubmed y en las bases de datos de publicaciones científicas indexadas: Biblioteca Electrónica Científica en Línea (Scielo), Literatura Latinoamericana y del Caribe en Ciencias de la Salud (LILACS), Base de Datos de Enfermería (BDENF) e Índice Acumulativo de Literatura de Enfermería y Salud Aliada (CINAHL) y PubMed Portal, utilizando los descriptores "Síndrome de Down", "Patologías", "Trisomy 21", "Discapacidad Intelectual" , "Manifestaciones clínicas". **Resultados:** se encontraron 696 artículos, de los cuales 24 fueron analizados en su totalidad, de los cuales se seleccionaron 9 artículos que comprendían la muestra de este examen. La mayoría de los estudios seleccionados midieron las peculiares características fenotípicas en individuos con esta anomalía, a saber: ojos oblicuos, orejas bajas, braquidactilia, hipotonía, estatura baja, braquicefalia, hendiduras oblicuas en el párpado, epicante, manchas de Brushfield en el iris, entre otros. **Conclusión:** es necesario tener atención regular y seguimiento de los profesionales de la salud sobre patologías malignas, enfermedades autoinmunes e inflamatorias que afectan a las personas con DS.

Descriptores: Síndrome de Down; Patologías; Trisomía 21; Discapacidad Intelectual; Manifestaciones clínicas.

Introduction

Down Syndrome (DS) is a numerical genetic alteration, which occurs during cell division, characterized by the addition of a chromosome in the chromosome pair 21 of human DNA, thus forming trisomy 21. This is due to failure to separate genetic material during egg preparation or, more rarely, during spermatogenesis. It is a syndrome where its occurrence is associated with a number of factors, such as: maternal age and genetic mosaicism – where the mother presents the characteristic trisomy genotype in part of her cells.[1]

This pathology has a unique and unmistakable phenotype. Individuals present with flattened face, oblique eyes with epicantic fold, insertion of the lower ears, lingual protusion, muscular hypotonia, ligament laxity, brachydactyly (short fingers) and variable cognitive deficits.[2-4]

Trisomy is responsible for some basic pathologies, defined strictly by phenotypic expressions, among them, some more recurrent (such as hypotonia, heart disease[6], and vision disorders[7]: myopia, hyperopia and astigmatism).

In addition to these deleterious effects, this syndrome causes individuals greater susceptibility to respiratory diseases[10], especially low immunity directly linked to the genetic anomaly.[10]

Corroborating, an international study pointed out that a large number of people with DS develop neurological diseases such as Alzheimer's throughout their lives, precisely because of the characteristic of trisomy that causes an overexpression of the amyloid precursor protein (APP) - the sea coded by APP, due to the location of this extra gene in the pair of chromosomes 21.[11]

In a randomized clinical trial conducted in Argentina[14], it was observed that individuals with DS present, mostly, dental and stomatognathic disorders. The authors showed that the various alterations in breathing and swallowing have a significant impact on the development of the stomatognathic system, and it is essential to follow up professionals in the field of speech therapy, orthopedics and orthodontics.[14]

However, to evidence these pathologies associated with DS in a literature review is relevant, as it provides support for the elaboration of actions and acquisition of knowledge directed to the collectivity and health teams in order to minimize the problems resulting from disorders associated with trisomy, promoting a better quality of life to individuals with these genetic characteristics.

In the light of these findings, this study was based on the following review question: "what are the main pathologies associated with DS described in the literature?" In this sense, the aim of the study was to identify through a narrative review the most recurrent pathologies in individuals with DS.

Method

It is a narrative literature review, according to Rother[15], this modality of review aims to elucidate the development or describe the "state of the art" of a given thematic approach, from a theoretical perspective. Although it does not strictly characterize the criteria used in the evaluation and selection of primary studies, this type of literature review promotes knowledge about a specific object of study.[15] In view of this conjuncture, narrative review is structured based on stages, which will be presented in sequence[8]:

Step I: "elaboration of the guide question". The definition of the question that will guide the review determines which studies will be included, the means adopted for identification and the information collected from each selected record.[8]

Step II: "search or sampling in the literature". This stage is intrinsically related to the previous phase. The search in the databases should include the search in electronic databases, manual search in journals, through references described in the selected studies and the use of unpublished material (gray literature). The determination of inclusion and exclusion criteria should be carried out in accordance with the review question, considering the participants, any interventions and the results presented in the selected articles.[8]

Step III: "data collection". To extract data from selected articles, the following includes: definition of the study sample, method, sample calculation, measurement of variables and concepts used in manuscripts.[8]

Step IV: the "critical analysis of the included studies" is similar to the analysis of the data from the field research. At this stage, the articles are analyzed and the selection is made after careful reading of the titles and abstracts, excluding those records that did not meet the proposed theme. Finally, the text is read in its entirety for the selection of the sample that characterizes the narrative review.

Step V: "discussion of results". At this stage, we seek to interpret and synthesize the results of the selected studies and identify the possible gaps in the literature.[8]

Step VI: "presentation of narrative review". The presentation of the review should be clear and complete to allow the reader to critically evaluate the results. It should contain, then, pertinent and detailed information, based on contextualized methodologies, without omitting any related evidence.[8]

For this review, a survey of the literature was conducted in the Pubmed Portal and in the databases of indexed scientific publications: Scientific Electronic Library Online (Scielo), Latin American and Caribbean Literature on Health Sciences (LILACS), Nursing Database (BDENF) and Cumulative Index to Nursing and Allied Health Literature (CINAHL) and PubMed Portal, in order to identify studies that measured the main pathologies that affect people with DS.

The Descriptors in Health Sciences - VHL were: "Down's syndrome" AND "Pathologies" AND "Trisomy 21" AND "Intellectual Disability" AND "Clinical manifestations". The searches were carried out in April 2021, followed by the analysis of the words of the text contained in the title and abstract and the indexed terms used to describe the article. Articles published in the Portuguese, English and Spanish, with different research designs, were analyzed to obtain a comprehensive understanding of the phenomenon investigated. To this end, and due to the contemporary aspects of the theme investigated, the period of publication of the studies found was not limited.

The criteria adopted for the inclusion of the articles were: full availability of the text in digital environment (open access) and thematic relevance. However, the following were excluded: articles that analyzed only the effects of medications on the main pathologies that affect people with DS, those who evaluated only the cost-effectiveness of treatments and the investigations performed in patients who did not present pathologies associated with Trisomy.

Results

For the bibliographic survey, a search was conducted in three databases and in the PubMed Portal, as shown in Table 1.

Table 1 - Databases consulted using descriptors. Sao Paulo, 2020.

Database	n	%
CINAHL	274	40,53
PubMed	239	35,35
BDENF E LILACS	163	24,11
TOTAL	676	100

Initially, 676 references were identified with the search in the databases, and 85 duplicate articles were removed. After this exclusion, the titles and abstracts of the 591 articles were read. After this stage, 567 manuscripts were excluded because they did not meet the selection criteria. Therefore, 24 articles were read in full. For eligibility, 15 studies were withdrawn because they did not meet the established criteria, so 9 articles that comprised the sample of this review were selected.

Table 2 shows that, after applying the criteria related to the method adopted in this review, 4 articles indexed in lilacs database were selected, 3 articles in Scielo and 2 manuscripts in PubMed, totaling 9 articles.

Table 2 - Databases used in the extraction of articles. Sao Paulo, 2020.

Database	n	%
LILACS	4	44,44
Scielo	3	33,33
PubMed	2	22,22
TOTAL	9	100

Table 3 shows that in 2014 the largest number of publications on the subject of this review was concentrated, corresponding to four published articles (44.44%).

Table 3 - Selected publications for sample composition, second year of indexing. Sao Paulo, 2020.

Year of publication	Absolute number	Porcentage (%)
2013	01	11,1
2014	04	44,4
2016	02	22,2
2019	02	22,2
TOTAL	9	100

Finally, table 4 shows the articles selected according to title, authors, year of publication and journal.

Table 4 - Articles included in the review**.** Sao Paulo, 2020.

Title of article	Authors	Year	Journal
An overview of respiratory problems in children with Down's syndrome[10]	Rachel Watts H Vyas	2013	BMJ
Major congenital anomalies in babies born with Down syndrome: a EUROCAT population-based registry study[12]	Joan K. Morris, Ester Garne, Diana Wellesley, et al.	2014	American Journal of Medical Genetics
Peripheral auditory evaluation in children with Down syndrome [13]	Barbara Carrico Alessandra Giannella Samelli Carla Gentile Matas, et al.	2014	Brazilian Academy of Audiology
Congenital heart diseases and chromosome stoopathies detected by karyotype[6]	Patrícia Trevisan Rafael Fabiano M. Rosa Dayane Bohn Koshiyama, et al.	2014	Paulista Journal of Pediatrics
Prevalence and profile of congenital heart diseases and pulmonary hypertension in Down syndrome in pediatric cardiology service[2]	Felipe Alves Mourato Lúcia Roberta R. Villachan Sandra da Silva Mattos	2014	Paulista Journal of Pediatrics
Down's syndrome[9]	Doreen Crawford Annette Dearmun	2016	Evidence & Practice / A-Z of syndromes
Motor Development Assessment in Children with Down Syndrome[5]	André Soares Trindade Marcos Antonio do Nascimento	2016	Brazilian Journal of Special Education
Dementia in Down syndrome: unique insights for Alzheimer disease research[11]	Ira T Lott Elizabeth Head	2019	Nature Reviews Neurology
Par XXI trisomy: Stomatopathic features[14]	Carolina Astegiano Antonella Boiardi Juan Pablo Cacioli, et al.	2019	Rev. Soc. Odontol. La Plata

Discussion

This review showed the expressive interest in investigating the most recurrent pathologies in individuals with DS, considering their impacts on the life of this population. The nine selected studies provided important indicators of these comorbidities, constituting an essential basis for understanding the most common genetic abnormalities globally.[9]

Most of the selected studies[2,6,10-14] measured the peculiar phenotypic characteristics in individuals with this anomaly, the following: oblique eyes, low ears, brachydactyly, hypotonia, short stature, brachycephaly, oblique fissures in the eyelid, epicanth, Brushfield spots on the iris, protruding tongue, small ears, small and wide hands, clinodactyly of the fifth finger, apes wrinkle and moderate to severe intellectual disability, gastrointestinal and cardiac malformations ,

marked increase in the incidence of leukemia and early onset of Alzheimer's. In addition to these aspects, people with DS may be affected by other pathologies associated with this genetic condition that commonly reduces life expectancy.

A European investigation pointed out that, among the pathologies associated with trisomy, more than 40% of babies born with DS had congenital heart diseases.[12] This study conducted with 29 researchers had as main objective to reveal whether the introduction of prenatal genetic screening programs influences any type of decline in the prevalence of additional anomalies in babies with DS.[12] Regarding congenital heart disease.12 Regarding congenital heart disease, it was inferred that, even with the great advance in diagnostic techniques, karyotype examination (study of chromosomes present in DNA), is still essential to detect a congenital heart disease early.[6-12]

This syndrome causes greater susceptibility to respiratory diseases in individuals, mainly due to low immunity directly associated with the genetic anomaly.[10] Regarding impairment in the immune system, national and international studies[10,13,18] analyzed peripheral hearing in children with DS. As results, it was evidenced that, although they did not observe significant divergences, the findings were suggestive of impairment of cochlear function, possibly related to frequent otitis, which may cause severe health damage when not properly treated.

In addition, it was identified in a study conducted with 77 people with DS, who during the 20-year period, 97.4% of people developed dementia. Clinical dementia was associated with cognitive and functional deficit and epileptic seizures. From this perspective, the risk of dementia increased from 23% in people aged 50 to 80% in people aged 65 years and over.[17]

A Brazilian study tested the fine motor skills, balance and temporal organization of seven children with DS. It was found that the level of motor delay varied according to the requested task, respecting the uniqueness of each child, however, it was evidenced that all participants of the research presented deficits in their motor capacity.[5]

Finally, by summing up the information obtained through the articles included in this review, it is evident that most of the most recurrent pathologies in individuals with DS are directly associated with immunological deficiencies and genotypic or phenotypic alterations related to trisomy. In order to promote quality of life for people with DS, it is suggested that trisomy should be managed by trained health professionals and caregivers with skills - willing to resignify care in a humanized and thorough way. Thus, the deleterious effects and complications arising from these genetic mutations can be reduced and life expectancy maximized.

Conclusion

Individuals with Down syndrome suffer from a variety of immunological diseases and mediated conditions that significantly impact their quality of life. Apparently, all components of your immune system present abnormalities and correlations between these clinical changes. Therefore, the resources and therapy for this population remains challenging for health services at all levels of care.

However, regarding the clinical care of individuals with DS, one should consider the complexity of this condition and the numerous factors (mainly

immunological) that contribute to a higher risk of infections and pathologies associated with trisomy 21. In this sense, it is necessary to have regular attention and follow-up of health professionals about malignant pathologies, autoimmune and inflammatory diseases that affect people with DS.

However, further research is needed to understand the most recurrent pathologies associated with trisomy and the correlation with clinical manifestations, as well as studies to investigate possible strategies of treatment and prophylactic therapy that favor the immune system of these individuals, providing them with a better state of health and quality of life, since these cannot be neglected.

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