

DOWN SYNDROME IN ADULTS: SUCCESS AND CHALLENGE

Síndrome de Down em adultos: sucessos e desafios

Milton Luiz Gorzoni^a , Carla Franchi Pinto^a , Aleksandro Ferreira^a 

ABSTRACT

The estimated average survival of people with Down syndrome (DS) is currently over 50 years of age. This demographic finding warrants attention of health professionals who will care for an increasing number of adults with DS. Clinical evaluation of adults with DS should correlate characteristics inherent to the age group, especially the peculiarities produced by the syndrome. The present article proposes the development of preventive and vaccination programs — according to gender and age — and screening of diseases and conditions associated with the syndrome: 1) endocrine diseases; 2) cardiac diseases; 3) mental health; 4) dental care; 5) sensory organs; 6) osteoarticular abnormalities; 7) skin and appendages; 8) gastrointestinal diseases; and 9) cancer. However, there is scant information on the impact of comorbidities on life expectancy and quality of life or on the social and hospital costs of adults with DS.

KEYWORDS: Down syndrome; adults; health care.

RESUMO

A estimativa da sobrevivência média de indivíduos com síndrome de Down (SD) passa atualmente dos 50 anos de idade. Esse dado demográfico justifica a atenção de profissionais da saúde que prestarão cuidados a um número crescente de adultos com SD. A avaliação clínica desse grupo de pacientes adultos deve correlacionar características inerentes à faixa etária, principalmente as peculiaridades produzidas pela síndrome. O presente artigo propõe o desenvolvimento de programas de prevenção e vacinação — conforme gênero e idade — e triagem de doenças e quadros associados à síndrome: 1) doenças endócrinas; 2) doenças cardíacas; 3) saúde mental; 4) saúde bucal; 5) órgãos sensoriais; 6) anomalias osteoarticulares; 7) pele e anexos; 8) doenças gastrointestinais; 9) câncer. Entretanto, há poucas informações sobre o impacto das comorbidades na expectativa de vida e na qualidade de vida, além dos custos hospitalares e sociais de adultos com SD.

PALAVRAS-CHAVE: síndrome de Down; adultos; atenção à saúde.

^aIrmãdade da Santa Casa de Misericórdia de São Paulo, Faculdade de Ciências Médicas da Santa Casa de São Paulo – São Paulo (SP), Brazil.

Corresponding data

Milton Luiz Gorzoni – Departamento de Clínica Médica, Faculdade de Ciências Médicas da Santa Casa de São Paulo – Rua Doutor Cesário Motta Júnior, 112 – CEP: 01221-020 – São Paulo (SP), Brasil. E-mail: gorzoni@uol.com.br

Received on: 03/21/2019. Accepted on: 04/17/2019

DOI: 10.5327/Z2447-211520191900022

INTRODUCTION

In 1866, John Langdon Haydon Down, medical superintendent at the Royal Earlswood Asylum for Idiots between 1855 and 1868, published *Observations on an Ethnic Classification of Idiots*, reporting that over 10% of children in his care presented a phenotypic resemblance — irrespective of ethnicity — to mongols.^{1,2} Initially called mongolism, following the 1959 study conducted by Lejeune et al.³ reporting chromosome 21 (trisomy), the condition was renamed trisomy 21 or Down syndrome (DS), after the individual who first described it, thereby avoiding any ethnic references.⁴

The period spanning from the 19th century — when the most common cause of death of children with DS was tuberculosis¹ — to the 21st century has seen a number of advances prolonging the lives of individuals with trisomy 21. This trend warrants attention of health professionals and those involved in child care and pediatrics.

Life expectancy

Some 70 years ago, the average survival of persons with DS was around 12 years of age.⁵ Since then, mean and median age at death in this group have risen dramatically and by 2007 were 47.3 and 53 years, respectively. This shift represents a 3.75-fold increase in life expectancy of individuals with DS between 1970 and 2007.⁶ Reports on longevity have changed from description of single cases to statistics of prevalence in adults and older adults.^{7,8}

Although beyond the scope of the present article, it is noteworthy that aging of individuals with DS is part of the aging process of the population as a whole. This process has resulted from new preventive, diagnostic, therapeutic and rehabilitation actions which have allowed a growing contingent of adults to survive into older age.⁹

Clinical assessment of adults with Down Syndrome

Health professionals should be aware that people with DS require specific clinical assessments according to age group with an emphasis on the peculiarities produced by the syndrome. Therefore, preventive and vaccination programs should be developed — according to gender and age — as well as screening for diseases and conditions associated with the syndrome:

- endocrine diseases;
- cardiac diseases;
- mental health;
- dental care;
- sensory organs;
- osteoarticular abnormalities;
- skin and appendages;

- gastrointestinal diseases;
- cancer.¹⁰

Endocrine diseases

The high prevalence of overweight and obesity in adults with DS warrants attention. In a study conducted by Pucci et al.¹¹ of 97 adults with DS, 40.7% were overweight and 37.4% were obese. The study found no significant differences for gender or age (18–56 years).

A high prevalence of thyroid disease associated with changes in serum levels of thyroid stimulating hormone (TSH) and anti-thyroid peroxidase (anti-TPO) antibodies has also been reported, particularly in individuals above 9 years of age.¹² Regular assessment of thyroid function is recommended in patients with DS to reduce obesity and cognitive deficits in this population.^{13,14}

Similar attention should be paid to glycemic changes, particularly type I diabetes mellitus, given that the prevalence of diabetes in patients with DS is approximately four times higher than that in the general population.¹⁵ Anwar et al.¹⁶ suggested that, owing to the habitually stable lifestyle of individuals with DS, simpler insulin therapy plans can provide satisfactory glycemic control. The small sample of the study calls for caution before generalizing this clinical finding, and further studies involving a greater number of diabetic patients with DS are needed to confirm these data.

DS and associated comorbidities promote lower rate of growth with stunting after puberty. Average height of both men and women with DS is 1.5 to 4 standard deviations lower than the average for the general population. This calls for regular use of specific growth curves in people with the syndrome.^{17,18}

Patients with DS are often diagnosed with primary or partial gonadal deficiency, a condition normally detected in adults. Women with DS are predisposed to premature ovarian insufficiency and early menopause, whereas men exhibit subfertility or sterility and hypogonadism. There are reports, however, of procreative ability in individuals of both sexes with DS. Ignorance of the full sexual act may be a factor contributing to the low fertility rates reported among adults with DS.^{19–22}

Low bone density in adults with DS is correlated with significant reductions in osteoblastic bone formation and inadequate development of bone mass. Hypotonia, low level of physical activity, non-ideal calcium intake and low serum vitamin D concentrations are also commonly associated with the syndrome. The abovementioned hormonal factors and the chronic use of anticonvulsants are also involved in the underlying mechanisms. These observations raise questions

over prescribing anti-absorptive bone therapy in this population and suggest the use of other interventions — such as regular physical activity — as a means of increasing bone density in adults with DS.²³⁻²⁵

Cardiac diseases

There is a strong association between genetic and cardiovascular abnormalities, especially structural congenital cardiac diseases (cardiac valvular or myocardial abnormalities or defects). An estimated half of all patients with DS have congenital heart diseases, and most cases with significant hemodynamic changes are managed surgically during childhood.^{26,27}

Depending on the underlying heart disease, residual atrial or ventricular changes, valvular regurgitations and stenosis of surgically corrected valves may persist in adults with DS. There are also reports of atrioventricular blocks and bradycardia causing progressive limitation to physical exercise. Regular cardiovascular assessment is recommended in adults with DS — with or without history of heart diseases — owing to the frequent findings of mitral valve prolapse, regurgitation in aortic, mitral and tricuspid valves, and heart failure. As part of this assessment, it is also prudent to perform an echocardiogram every five years and administer infective endocarditis prophylactic antibiotics in the event of surgical and dental procedures.²⁶⁻²⁸

Mental health

An estimated 30% of people with DS have mental health disorders. The spectrum of these conditions includes depressive processes, obsessive-compulsive disorders, behavioral disorders and early dementia.¹⁰

Factors triggering depression should be investigated in people with DS that exhibit a decline in function or self-care. Situations such as loss of family members or friends and/or changes in school, work or social structure are risk factors for triggering depressive symptoms. Similarly, the use of medications such as phenobarbital, benzodiazepines, beta-blockers and statins can also induce symptoms of depression. Serotonin uptake inhibitors offer greater efficacy than tricyclic antidepressants for treating depression in this population. This can be explained by the high level of anticholinergic adverse reactions caused by the latter group of antidepressants in patients with DS.^{10,29}

Self-talk is commonly observed in people with DS, particularly in situations of stress. Professionals should be alert to this symptom so as not to mistake it for hallucinatory behavior in adults with DS. There are also reports of catatonic conditions in adolescents and young adults without a

clear cause, yet reversible in nature. These two symptoms — self-talk and catatonia — deserve special attention given that schizophrenia and psychosis rarely occur in individuals with DS.^{10,30}

Conversely, the prevalence of Alzheimer disease is progressive as this population ages. Reported rates are 0–10% in patients aged 30–39 years, 10–25% in those aged 40–49 years and 28–55% in those aged 50–59 years. However, prior to establishing a definitive diagnosis of cognitive dysfunction, it must be differentiated from depressive conditions, thyroid diseases, epilepsy and hearing and/or visual deficits. As in the general population, Alzheimer disease is a diagnosis of exclusion in people with DS. The symptoms of dementia in adults with DS include — besides cognitive decline — behavioral changes, functional decline, sleep and gait disturbances, seizures and incontinence.^{10,31,32}

Some scholars have discussed the possibility of assessing gait in adults with DS as an early marker of cognitive decline and Alzheimer disease. Dyspraxia often manifests during the onset of dementia both in the general population and in patients with DS. Gait dyspraxia is defined as the progressive loss of full use of the lower limbs in the act of walking, when this deficit cannot be attributed to other causes such as sensory changes, poor coordination or muscle weakness. Easily identified during a clinical exam, this manifestation serves as a measure of the evolution of cognitive dysfunction, especially in the absence of other neurological signs.^{33,34}

But how can people with DS be cognitively assessed? Traditional neuropsychological tests and imaging methods are unable to reliably diagnose or differentiate dementia and depression.³² Deb et al.³³ proposed the use of the Dementia Screening Questionnaire for Individuals with Intellectual Disabilities (DSQIID), considered easy to administer in adults with DS. However, they were unable to define a cut-off score for screening dementia in people with severe intellectual disabilities. Carvalho et al.³⁵ analyzed linguistic profile in DS using the Arizona Battery for Communication Disorders of Dementia (ABCD) and deemed the profile similar to that of individuals with Alzheimer disease. This was a pilot study based on a small sample (30 adults with DS) and the authors concluded that the investigation should be expanded to confirm the initial findings. Thus, cognitive assessments for adults with DS remain at a development and clinical assessment stage.

The process and technique of caring for adults with DS in association with Alzheimer disease does not differ from that of patients in the general population. Given that in many cases it is difficult to differentiate dementia from depression, trial treatment with serotonin uptake inhibitors can be useful.¹⁰

Dental care

Patients with DS should be provided with guidance on proper oral hygiene in view of the high rate of gingivitis and periodontal diseases in this population. Anticonvulsant medications such as phenytoin can induce gingival changes and the association of poor oral health with valve injury, posing a permanent risk of infective endocarditis in adults with DS. Six-monthly dental assessments are recommended to maintain oral cavity health for phonation and deglutition and preserve the dental arch.^{10,27,36,37}

Sensory organs

The prevalence of hearing deficits in adults with DS is around 70% and increases with age. Almost 100% of individuals with DS aged 60 years or older have hearing problems. These rates exceed those found in older adults without DS. This is important because hearing loss can lead to social isolation, low self-esteem, functional decline, delirium and depression. Deafness can also impact speech disorders — common in people with DS — and can contribute to situations where, when unresponsive to requests they cannot hear, adults with DS are labeled “difficult”.^{10,38,39}

There are various methods for carrying out a preliminary evaluation of hearing ability, although no consensus exists on the best screening method for hearing loss in clinical practice. These are individualized assessments — often for adults with DS unable to verbalize the information requested in these complementary exams — and, therefore, the cost/benefit and frequency of hearing screening lack well defined proposals or routines. Hearing assessments are recommended every two years in adults with DS.^{10,38,39}

Radiologic observation of malformation of the inner ear and dysplasia of the temporal bone in people with DS has become a focus of analysis with regard to correlation with hearing loss in this population. Likewise, history of otitis media or cholesteatoma during childhood warrants investigation.^{38,39} As adults with DS can also present cerumen plugs, otoscopy should be part of the clinical assessment of these patients.^{40,41}

Visual deficits and ocular anomalies are also frequent in adults and older adults with DS. Visual loss tends to occur earlier and to have a more rapid onset in adults with DS than in those without the syndrome. Although the prevalence of severe visual deficit is estimated at around 45% in adults with DS aged 50–59 years, a little over half of these cases are diagnosed and only 50% of individuals with DS have corrected eyesight.^{39,40,41}

When detected, the most common ocular problems among adults with DS include refraction, strabismus, cataracts

and keratoconus. The prevalence of cataracts increases with age in people with DS, being comparable or greater than that found in the general population. Even after cataract surgery, there is a risk of persistence of impaired visual acuity due to other ocular dysfunctions. Adults with DS develop senile cataracts earlier than healthy adults of the same age, a phenomenon attributed to accelerated aging caused by DS. Akin to hearing assessments, ophthalmologic assessments are also recommended every two years in adults with DS.^{31,36,39,41}

Osteoarticular abnormalities

Cervical spine abnormalities are common in people with DS. Atlantoaxial instability — with risk of upper cervical spinal cord injury — is the most frequently reported problem. Complaints of neck pain, gait deficits and changes in bowel or bladder function associated with increased deep tendon reflexes, Babinski sign and loss of muscle strength in upper or lower limbs are relevant signs and symptoms in atlantoaxial subluxation.^{10,36,38,41,42}

Other associations of DS and cervical myelopathy arise from changes in the odontoid process or in atlanto-occipital articulation and due to hypoplasia of the posterior arch of the first cervical vertebra (C1). Young adults with DS may also present degenerative abnormalities in the mid and lower portions of the cervical spine with potential for the development of progressive myelopathy. There are no significant gender differences regarding these abnormalities.^{36,38,41,42}

Also observed is a tendency for ligament laxity, a situation which triggers acquired hip or patella luxation and flat foot ankle pronation. Other frequent clinical findings in adults with DS include detection of scoliosis and osteoarthritis.^{10,41}

Routine neurological examination exploring for upper motor neuron signs caused by spinal cord compression are recommended. There are also calls for inclusion of radiologic control of the cervical spine as a standard procedure in care centers attending this population.^{10,36,38,41,42}

Skin and appendages

Cutaneous manifestations associated with DS are frequently seen in clinical practice. Loss and/or graying of the hair and premature xerosis, solar damage and wrinkling of the skin consistent with accelerated aging are typical in adults with DS.^{39,43}

Skin diseases common in this age group are predominantly due to autoimmune conditions and infections. Some of these diseases can be attributed to progressive decline of self-care temporally associated with dementia states — particularly Alzheimer disease — in this population.^{39,43}

Atopic dermatitis is the most common example of autoimmune dermatosis in people with DS. It is a chronic inflammatory skin disease with possible involvement of genetic defect in proteins that maintain the barrier of the epidermis. Atopic cases may present with other dermatites or dermatoses, i.e., not all skin problems in these patients can be diagnosed as atopic dermatitis. Therefore, diagnosis may not be straightforward and be based on several signs and symptoms, hampering the establishment of homogenous clinical definitions. Hanifin and Rajka⁴⁴ developed practical criteria for diagnosis and standardization in clinical follow-up of these patients:

- major features:
 1. pruritus;
 2. typical cutaneous lesions and distribution: flexural lichenification or linearity in adults and facial extensor involvement in infants and children;
 3. chronic or chronically relapsing dermatitis;
 4. personal or family history of atopy (asthma, allergic rhinitis and/or atopic dermatitis);
- minor features:
 1. xerosis;
 2. ichthyosis/palmar hyperlinearity, pilaris keratosis;
 3. immediate (type 1) skin test reaction;
 4. elevated serum immunoglobulin E (IgE);
 5. early age of onset;
 6. tendency toward cutaneous infections (especially staph, aureus and herpes simplex), impaired cell-mediated immunity;
 7. tendency toward non-specific hand or foot dermatitis;
 8. nipple eczema;
 9. cheilitis;
 10. recurrent conjunctivitis;
 11. Dennie-Morgan infraorbital fold;
 12. keratoconus;
 13. anterior subcapsular cataracts;
 14. orbital darkening;
 15. facial pallor, facial erythema;
 16. pityriasis alba;
 17. anterior neck folds;
 18. itch when sweating;
 19. intolerance to wool and lipid solvents;
 20. perifollicular accentuation;
 21. food intolerance;
 22. course influenced by environmental and emotional factors;
 23. white dermographism, delayed blanch. Atopic dermatitis is diagnosed when three major and three minor features are met.^{43,44}

Another chronic dermatosis often found in adults with DS is seborrheic dermatitis, characterized by pruritus, scaling and erythema primarily in areas with a high concentration of sebaceous glands (scalp, face, thorax and buttocks). The condition occurs — in most cases — at 30–60 years of age, and is more prevalent in men than women. The course includes periods of remission and exacerbation, irrespective of treatment administered, where outbreaks are associated with emotional stress, fatigue and depression. The condition promotes esthetic changes, impacting the self-esteem and social life of affected individuals, although serious clinical complications are rare.⁴³

Attention should also be paid to acanthosis nigricans, which renders the skin darker, thicker and velvety in body folds and creases. It is often associated with diabetes mellitus, obesity and other endocrinologic disorders in adults with DS. It affects only the appearance of the skin and has no specific treatment. It should be noted, however, that weight loss in obese patients improves the skin status of those with the condition.⁴³

Skin assessments in adults with DS, given the proneness for immunodeficiency in this syndrome, should encompass situations such as fungal and bacterial infections and conditions such as scabies. The treatment approach is similar to that employed for the general population.^{39,43}

Gastrointestinal diseases

The association of celiac disease and DS should be noted, as an estimated 5% of people with DS have this autoimmune digestive disease. Chronic abdominal symptoms, even if unspecific such as pain or dyspepsia, mouth lesions and cutaneous eruptions, in many cases call for ordering specific blood tests, such as anti-transglutaminase antibodies (ATA) and/or antiendomysial antibodies (anti-EMA) and serum IgA. Adults with DS with thyroid diseases, type 1 diabetes mellitus or anemia should undergo annual blood tests.^{31,41}

People with DS commonly have intestinal obstipation complaints. If the symptom is severe, celiac disease and hypothyroidism should be investigated. Diet and sufficient physical activity can help improve this symptom in most DS patients. Gastroesophageal reflux disease is also more prevalent in the population with DS and usually responds to standard treatment for this infection.⁴¹

Cancer

Persons with DS have a 10- to 30-fold greater risk for developing leukemia than the general population. Given that trisomy 21 is the most common defect in tumoral cells of acute

non-lymphoblastic leukemia, it is believed that the additional chromosome 21 induces susceptibility to this type of leukemia. This hypothesis was later confirmed by identification of various oncogenes on the long arm of chromosome 21.^{39,45}

The association of DS with other kinds of cancer — besides leukemia — includes greater risk for lymphomas, testicular carcinoma, retinoblastoma and extragonadal germ cell tumors. There are, however, cancers with lower incidence in persons with DS, such as tumors of the central and peripheral nervous system, cancer of the lung and upper airways, urinary tract tumors, endometrial adenocarcinoma and breast cancer. There is also a propensity for developing cancer at an early age compared to the general population. Men with DS are more susceptible to some cancers — such as lymphomas and leukemia — than women with the syndrome.^{10,36,39,45,46}

Besides genetic aspects, a number of theories have been proposed to explain the higher or lower risks of different kinds of cancer in persons with DS. Obesity and lower level of physical activity in adults with DS are thought to contribute to the development of cancer. Conversely, lower exposure to environmental factors, early menopause, and low alcohol and tobacco use may reduce the risk of some cancers in this population. Analytic studies of cancer and DS are scarce, particularly investigations into the increased survival of this population, a demographic process that is changing the pattern of cancer types observed in adults with DS.^{36,39}

Signs and symptoms suggestive of leukemia and lymphomas, such as refractory anemia, lethargy, fever of unknown cause, arthralgia, pallor, lymphadenomegaly, recurrent spontaneous bleeding and hematomas should be initially investigated

by a complete blood count test. Annual testicular, retinal and breast examinations are recommended.^{36,41}

DS and outpatient care

Health professionals should address the individual with DS directly, avoiding indirect contact through a guardian or a caregiver. This allows an assessment of expressive language of the patient and the development of a relationship of trust between the person with DS, the family and/or caregiver and the professionals involved in outpatient care. This creates a conducive setting for successful implementation of the therapy plan proposed. Motivated multiprofessional teams and the right environment for proper outpatient treatment increase the likelihood of adults with DS experiencing healthy aging in the future.¹⁰

CONCLUSIONS

Gaps in the literature on adults with DS are evident. Many articles are descriptive and involve only small convenience samples without control groups. Scant information is available on the impact of comorbidities on life expectancy and quality of life or on social and hospital costs in adults with DS. The conclusions are based on a recent, sharp rise in the number of people with DS in this age group¹⁷. Hence, this age group can be deemed both a success and a challenge in terms of further investigations and clinical research.

CONFLICT OF INTERESTS

The authors declare no conflict of interests.

REFERENCES

1. Ward OC. A Victorian children's charity asylum and a private care-home: mortality and morbidity compared. *Arch Dis Child*. 2002;86(Suppl. 1):A52.
2. Down JH. Observations on an Ethnic Classification of Idiots. 1866. *Ment Retard*. 1995;33(1):54-6.
3. Lejeune J, Turpin R, Gautier MM. Le mongolisme premier exemple d'aberration autosomique humaine. *Ann Génétique*. 1959;1(2):41-9.
4. Allen G, Benda CE, Böök JA, Carter CO, Ford CE, Chu EHY, et al. Mongolism. *Lancet*. 1961;277(7180):775. [https://doi.org/10.1016/S0140-6736\(61\)92939-7](https://doi.org/10.1016/S0140-6736(61)92939-7)
5. Penrose LS. The incidence of mongolism in the general population. *J Ment Sci*. 1949;95(400):685-8.
6. Presson AP, Partyka G, Jensen KM, Devine OJ, Rasmussen SA, McCabe LL, et al. Current Estimate of Down Syndrome Population Prevalence in the United States. *J Pediatr*. 2013;163(4):1163-8. <https://doi.org/10.1016/j.jpeds.2013.06.013>
7. Chicoine B, McGuire D. Longevity of a woman with Down syndrome: a case study. *Mental Retardation*. 1977;35(6):477-9. [https://doi.org/10.1352/0047-6765\(1997\)035%3C0477:LOAWWD%3E2.0.CO;2](https://doi.org/10.1352/0047-6765(1997)035%3C0477:LOAWWD%3E2.0.CO;2)
8. Wu J, Morris JK. The population prevalence of Down's syndrome in England and Wales in 2011. *Eur J Hum Genet*. 2013;21(9):1016-9. <https://doi.org/10.1038/ejhg.2012.294>
9. Veras R. Envelhecimento populacional contemporâneo: demandas, desafios e inovações. *Rev Saúde Pública*. 2009;43(3):548-54. <http://dx.doi.org/10.1590/S0034-89102009005000025>
10. Smith DS. Health Care Management of Adults with Down Syndrome. *Am Fam Physician*. 2001;64(6):1031-9.
11. Pucci F, Machado G, Solera E, Cenovicz F, Arruda C, Braga C, et al. Blood pressure levels and body mass index in Brazilian adults with Down syndrome. *São Paulo Med J*. 2016;134(4):330-4. <http://dx.doi.org/10.1590/1516-3180.2016.0057180316>
12. Nishihara RM, Utiyama SRR, Fiedler PT, Oliveira NP, Kotze LMS, Messias-Reason I. Alterações do TSH em pacientes com síndrome de Down: uma interpretação nem sempre fácil. *J Bras Patol Med Lab*. 2006;42(5):339-43. <http://dx.doi.org/10.1590/S1676-24442006000500005>
13. Lavigne J, Sharr C, Elsharkawi I, Ozonoff A, Baumer N, Brasington C, et al. Thyroid dysfunction in patients with Down syndrome: Results from a multi-institutional registry study. *Am J Med Genet A*. 2017;173(6):1539-45. <https://doi.org/10.1002/ajmg.a.38219>

14. Percy ME, Dalton AJ, Markovic VD, Crapper McLachlan DR, Gera E, Hummel JT, et al. Autoimmune thyroiditis associated with mild "subclinical" hypothyroidism in adults with Down syndrome: a comparison of patients with and without manifestations of Alzheimer disease. *Am J Med Genet.* 1990;36(2):148-54. <https://doi.org/10.1002/ajmg.1320360205>
15. Bergholdt R, Eising S, Nerup J, Pociot F. Increased prevalence of Down's syndrome in individuals with type 1 diabetes in Denmark: A nationwide population-based study. *Diabetologia.* 2006;49(6):1179-82. <https://doi.org/10.1007/s00125-006-0231-6>
16. Anwar AJ, Walker JD, Frier BM. Type 1 diabetes mellitus and Down's syndrome: prevalence, management and diabetic complications. *Diabet Med.* 1998;15(2):160-3. [https://doi.org/10.1002/\(SICI\)1096-9136\(199802\)15:2%3C160::AID-DIA537%3E3.0.CO;2-J](https://doi.org/10.1002/(SICI)1096-9136(199802)15:2%3C160::AID-DIA537%3E3.0.CO;2-J)
17. Gorla JI, Duarte E, Costa LT, Freire F. Crescimento de crianças e adolescentes com Síndrome de Down – Uma breve revisão de literatura. *Rev Bras Cineantropom Desempenho Hum.* 2011;13(3):230-7. <http://dx.doi.org/10.5007/1980-0037.2011v13n3p230>
18. Bravo-Valenzuela NJM, Passarelli MLB, Coates MV. Curvas de crescimento pômulo-estatural em crianças com síndrome de Down: uma revisão sistemática. *Rev Paul Pediatr.* 2011;29(2):261-9. <http://dx.doi.org/10.1590/S0103-05822011000200019>
19. Hsiang YH, Berkovitz GD, Bland GL, Migeon CJ, Warren AC. Gonadal function in patients with Down syndrome. *Am J Med Genet.* 1987;27(2):449-58. <https://doi.org/10.1002/ajmg.1320270223>
20. Romualdi D, Proto C, De Cicco S, Immediata V, Barone C, Romano C, et al. Low AMH levels as a marker of reduce ovarian reserve in young women affected by Down's syndrome. *Menopause.* 2016;23(11):1247-51. <https://doi.org/10.1097/GME.0000000000000695>
21. Zühlke C, Thies U, Braulke I, Reis A, Schirren C. Down syndrome and male fertility: PCR-derived fingerprinting, serological and andrological investigations. *Clin Genet.* 1994;46(4):324-6.
22. Pradhan M, Dalal A, Khan F, Agrawal S. Fertility in men with Down syndrome: a case report. *Fertil Steril.* 2006;86(6):1765.e1-3. <https://doi.org/10.1016/j.fertnstert.2006.03.071>
23. McKelvey KD, Fowler TW, Akel NS, Kelsay JA, Gaddy D, Wenger GR, et al. Low bone turnover and low bone density in a cohort of adults with Down syndrome. *Osteoporos Int.* 2013;24(4):1333-8. <https://doi.org/10.1007/s00198-012-2109-4>
24. Stagi S, Iurato C, Lapi E, Cavalli L, Brandi ML, Martino M. Bone status in genetics syndromes: A review. *Hormones.* 2015;14(1):19-31. <https://doi.org/10.1007/BF03401378>
25. Matute-Llorente Á, Gonzáles-Agüero A, Gómez-Cabello A, Vicente-Rodríguez G, Casajús JA. Decreased levels of physical activity in adolescents with down syndrome are related with low bone mineral density: a cross-sectional study. *BMC Endocr Disord.* 2013;13:22. <https://doi.org/10.1186/1472-6823-13-22>
26. Lin AE, Basson CT, Goldmuntz E, Magoulas PL, McDermott DA, McDonald-McGinn DM, et al. Adults with genetic syndromes and cardiovascular abnormalities: Clinical history and management. *Genet Med.* 2008;10(7):469-94. <https://doi.org/10.1097/GIM.0b013e3181772111>
27. British Cardiac Society Working Party. Grown-up congenital heart (GUCH) disease: current needs and provision of service for adolescents and adults with congenital heart disease in the UK. *Heart.* 2002;88(Suppl. 1):i1-14. https://doi.org/10.1136/heart.88.suppl_1.i1
28. Hamada T, Gejyo F, Koshino Y, Murata T, Omori M, Nishio M, et al. Echocardiographic evaluation of cardiac valvular abnormalities in adults with Down's syndrome. *Tohoku J Exp Med.* 1998;185(1):31-5.
29. Jain KK. Drug-induced neurological disorders. Seattle: Hogrefe & Huber; 1996. 60 p.
30. Ghaziuddin N, Nassiri A, Miles JH. Catatonia in Down syndrome; a treatable cause of regression. *Neuropsychiatr Dis Treat.* 2015;11:941-9. <https://dx.doi.org/10.2147%2FNDT.577307>
31. Henderson A, Lynch SA, Wilkinson S, Hunter M. Adults with Down's syndrome: the prevalence of complications and health care in the community. *Br J Gen Pract.* 2007;57(534):50-5.
32. Dekker AD, Strydom A, Coppus AMW, Nizetic D, Vermeiren Y, Naud PJW, et al. Behavioural and psychological symptoms of dementia in Down syndrome: Early indicators of clinical Alzheimer's disease? *Cortex.* 2015;73:36-61. <https://doi.org/10.1016/j.cortex.2015.07.032>
33. Deb S, Hare M, Prior L, Bhaumik S. Dementia screening questionnaire for individuals with intellectual disabilities. *Br J Psychiatry.* 2007;190:440-4. <https://doi.org/10.1192/bjp.bp.106.024984>
34. Anderson-Mooney AJ, Schmitt FA, Head E, Lott IT, Heilman KM. Gait dyspraxia as a clinical marker of cognitive decline in Down syndrome: A review of theory and proposed mechanisms. *Brain Cogn.* 2016;104:48-57. <https://doi.org/10.1016/j.bandc.2016.02.007>
35. Carvalho CL, Belan AFR, Castro LR, Radanovic M. Analysis of the linguistic profile in down syndrome using the arizona battery for communication disorders of dementia – a pilot study. *Codas.* 2018;30(2):e20170164. <https://doi.org/10.1590/2317-1782/20182017164>
36. Malt EA, Dahl RC, Haugsand TM, Ulvestad IH, Emilsen NM, Hansen B, et al. Health and disease in adults with Down syndrome. *Tidsskr Nor Laegeforen.* 2013;133(3):290-4. <https://doi.org/10.4045/tidsskr.12.0390>
37. Arya R, Gulati S. Phenytoin-induced gingival overgrowth. *Acta Neurol Scand.* 2012;125(3):149-55. <https://doi.org/10.1111/j.1600-0404.2011.01535.x>
38. Capone GT, Chicoine B, Bulova P, Stephens M, Hart S, Crissman B, et al. Co-occurring medical conditions in adults with Down syndrome: A systematic review toward the development of health care guidelines. *Am J Med Genet A.* 2018;176(1):116-33. <https://doi.org/10.1002/ajmg.a.38512>
39. Esbensen AJ. Health conditions associated with aging and end of life of adults with Down syndrome. *Int Rev Res Ment Retard.* 2010;39(C):107-26. [https://dx.doi.org/10.1016%2F50074-7750\(10\)39004-5](https://dx.doi.org/10.1016%2F50074-7750(10)39004-5)
40. Chicoine B, McGuire D, Hebein S, Gilly D. Development of a clinic for adults with Down Syndrome. *Ment Retard.* 1994;32(2):100-6.
41. Ross WT, Olsen M. Care of the adult patient with Down Syndrome. *South Med J.* 2014;107(11):715-21. <https://doi.org/10.14423/SMJ.0000000000000193>
42. Bosma GP, van Buchem MA, Voormolen JH, van Biezen FC, Brouwer OF. Cervical spondylarthrotic myelopathy with early onset in Down's syndrome: five cases and a review of the literature. *J Intellect Disabil Res.* 1999;43(Pt 4):283-8.
43. Dominguez-Cruz JJ, Bueno Delgado MA. Dermatological Manifestations of Down Syndrome. In: Dey S, editor. *Genetics and Etiology of Down Syndrome.* Rijeka: InTech; 2011. p. 197-208.
44. Hanifn JM, Rajka G. Diagnostic features of atopic dermatitis. *Acta Derm Venereol Suppl (Stockh).* 1980;92:44-7. <https://doi.org/10.2340/00015555924447>
45. Boker LK, Blumstein T, Sadetzki S, Luxenburg O, Litvak I, Akstein E, et al. Incidence of leukemia and other cancers in Down syndrome subjects in Israel. *Int J Cancer.* 2001;93(5):741-4.
46. Patja K, Pukkala E, Sund R, Iivanainen M, Kaski M. Cancer incidence of persons with Down syndrome in Finland: A population-based study. *Int J Cancer.* 2006;118(7):1769-72. <https://doi.org/10.1002/ijc.21518>