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Additional Health Care Recommendations for Children with Down Syndrome

Abstract

The American Academy of Pediatrics has previously described comorbidities and health care recommendations in Down syndrome. This review was conducted of topics that have not been included, previously, in published recommendations, or which have required updating. These topics are: neonatal hyperbilirubinemia, thyroid dysfunction, deglutition disorders, immunity, vaccination, pulmonary hypertension, Mellitus diabetes, dyslipidemias, hyperuricemia, vitamin D, oxidative stress, and autism.

Method: Searches were performed with CINAHL, Medline, EMBASE, PsycINFO, PubMed, LILACS, RIMA and BNI and assessed for methodological quality using the Joanna Briggs Institute tool.

Conclusion: The medical aspects presented in this article can be used to help healthcare professionals, to provide a better and more effective care with patients. The early detection of some comorbidities can improve prognosis and lower care´s cost for the complications then may cause.

Keywords: Down syndrome, health care, recommendations

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Introduction

In 1994, the American Academy of Pediatrics (AAP), under the auspices of the Committee on Genetics, issued its first guidelines for health care in DS and other genetic disorders,[1] and these were updated in 2011.[2] During the last ten years, guidelines of recommendations have been produced internationally, with minimal variations, whose objective is to maintain the health of this population through preventive medicine and the timely detection of the diseases to which it is susceptible.

The Down Syndrome Clinic of the National Institute of Pediatrics (INP) in Mexico City has 14 years of experience providing health care to more than 1000 patients. We adhere to international recommendations, which are summarized in Table 1. There are currently no methodologically rigorous guides to clinical practice. However, previously published recommendations have significantly improved the quality of life and prognosis for people with DS, and with the continuous development of new knowledge, an update of the medical guidelines is urgently needed. Over the time, in our experience working in the INP's Down Syndrome Clinic,[2-5] we have found a high prevalence of comorbidities in patients with DS that are not reported in previous recommendations, but that have been analyzed in scientific studies. For this reason, we have conducted this review to identify new health care interventions that complement those already established.

Table 1 International Recommendations for Patients with Down Syndrome

	American Academy of Pediatrics[5]	Programa Iberoamericano[6]	Mexico Down Network (Red Down México)[7]	Chile[8]
Cardiology	-At birth	-At birth -At 13 years	-At birth -In adolescence	-At birth -At 12 years
Ophthalmology	-At birth -Annually until 5 years -Every 2 years from 5 to 13 years -Every 3 years thereafter	-At birth -From 6 to 12 months -Annually until 5 years -Every 2 years from 5 to 13 years -Every 3 years thereafter	-At birth -From 6 months to 2 years in case of strabismus, NLDO, or nystagmus -Annually thereafter	-At 12 months -Annually thereafter

Table Continued...

	American Academy of Pediatrics[5]	**Programa Iberoamericano**[6]	**Mexico Down Network (Red Down México)**[7]	**Chile**[8]
Audiology	-Auditory screening at birth -Annually until 13 years -Every 2 years thereafter	-Auditory screening at birth -From 6 to 12 months -Annually thereafter until 5 years -Every 2 years from 5 to 13 years -Every 3 years thereafter	-Auditory screening at birth -At 6 months -At 12 months -Annually thereafter	-Auditory screening at birth -At 6 months -Annually from one to 5 years -Thereafter every 2 years until 12 years -Thereafter every 3 years
Thyroid	-Neonatal screening -From 6 to 12 months -Annually thereafter	-From 6 to 12 months -Annually thereafter	-Metabolic screening -At 6 months -At 12 months -Annually thereafter	-At birth -At 6 months -At 12 months -Annually thereafter
Complete blood count	-At birth -Annually	-At birth -At 6 months -Annual exam	-From 0 to 6 months -At 12 months -Annually thereafter	-At birth -At 12 months -Annually thereafter
Sleep study	-At 4 years -Inquire at every medical exam	-1 between 1 and 5 years -1 between 5 and 12 years -1 between 13 and 18 years	-Beginning at 2 years in case of clinical suspicion	-From 3 to 4 years
Dentistry		-1 exam between 1 and 5 years -Annual exam	-At teething -Every 6 months	-Beginning at 2 years -Annually thereafter

NLDO,Nasolacrimal Duct Obstruction

The following topics are addressed: hyperbilirubinemia in the newborn infant, thyroid dysfunction, deglutition disorders, immunity, vaccination, pulmonary hypertension, diabetes mellitus, dyslipidemias, hyperuricemia, vitamin D, oxidative stress and autism.

Method

A narrative review was therefore identified as an appropriate way to provide an overview of research, while also allowing an integrated and synthesized interpretation of both qualitative and quantitative evidence.[6]

Search method: Searches were performed between February and December 2018, and repeated in April 2019 with the following databases: CINAHL, Medline, EMBASE, PsycINFO, PubMed, LILACS, RIMA and BNI. These databases were chosen due to the breadth of cross disciplinary coverage. Furthermore, these databases search across national and international peer-reviewed journals. The following search terms were used: [“neonatal hyperbilirubinemia”] [“thyroid dysfunction”] [“deglutition disorders”] [“immunity”] [“vaccination”] [“pulmonary hypertension”] [“diabetes mellitus”] [“dyslipidemias”] [“hyperuricemia”] [“vitamin D”] [“oxidative stress”] [“autism”] AND [“down syndrome”].

Inclusion or exclusion criteria: Unpublished dissertations or nonpeer-reviewed articles were excluded. Language limiters were applied for articles published in English and Spanish. All study designs and both, quantitative and qualitative methodologies, were included. Titles and abstracts were individually screened for relevance. Articles which had not focused on Down syndrome and published before 1995 were omitted. Additional articles were located through hand searching the reference lists of papers which met the inclusion criteria.

Quality assessment: All articles which met the inclusion criteria were critically appraised and assessed for methodological quality using the Joanna Briggs Institute tool.

Hyperbilirubinemia in the newborn infant

Up to 55% of newborns with DS present hyperbilirubinemia.[7] The probable causes are ineffective erythropoiesis, polycythemia, and increased heme degradation. The triple dosage of genes on chromosome 21 is associated with a disruption in the superoxide dismutase (*SOD1*)/glutathione peroxidase (GPx) relationship, with a greater formation of free radicals responsible for premature tissue aging and greater production of lipid peroxidation, which decreases the useful life of erythrocytes.[7]

The incidence of cholestasis has been reported at more than 100 times that of the general population,[8] associated with a lack of intrahepatic bile ducts,[9] congenital hypothyroidism, transient myeloproliferative disorder and parenteral nutrition.[10]

Given the high risk of central nervous system (CNS) complications associated with hyperbilirubinemia prior to the closure of the blood-brain barrier, and their high prevalence in patients with DS, we recommend analysis of bilirubin levels for every newborn infant with DS in the first seven days of life.

Thyroid function

The incidence of congenital hypothyroidism in newborns with DS has been reported as 1:113,[11] that is, 25 times greater than in the general population.[12] Levels of Thyroid-Stimulating Hormone (TSH) have been observed at the upper limits and T4 at the lower limits with respect to control subjects,[13,14] which is consistent with results found in a study published by the INP.[15] Congenital hypothyroidism must be diagnosed early, as lack of treatment could increase the effects of intellectual disability. It has been reported that 50% of patients with DS that develop congenital hypothyroidism show normal metabolic screening.[16] For this reason, we recommend an additional complete thyroid profile in the first month of life and not only metabolic screening which usually only includes one biomarker.

Deglutition

The stomatognathic system, which comprises the functions of sucking, chewing, swallowing, and speaking, is affected in people with DS. Changes in the morphophysiology of the CNS may also contribute to an impairment in the modulation of the phases of deglutition.[17] In patients with DS there is an alteration in deglutition, primarily in the oral phase, that may be asymptomatic. Oral motor difficulties are present in up to 64% of patients and can continue until adulthood.[18] Pharyngeal dysphagia is reported in 57% of DS patients, of which 80% continue with the condition despite surgical intervention, to an average age of 7 years old. In contrast, premature infants and those with gastroesophageal reflux resolve this condition between 2 and 3 years of age.[19] Pulmonary aspiration occurs in 42% of children with DS, as opposed to 12% in children without this condition; 90% of those with aspiration present no cough or other symptomatology.[20] In the esophageal phase, anatomical malformations have been reported in 9% of patients[21] and should be ruled out. An upper gastrointestinal series is recommended as a first step in the presence of any obstructive symptomatology. Another series of common conditions for this population should also be ruled out, including gastroesophageal reflux, achalasia, and sensory disorders.[20] For all these reasons, there should be early evaluation of deglutition in all age groups, in order to minimize risks and provide transdisciplinary treatment as necessary, for example: posture correction, progressive introduction of food textures, myofunctional and sensory therapy.

Immunity and vaccines

DS is the genetic disorder most commonly associated with immunological problems,[21,22] including a reduced number of T and B lymphocytes, dysregulation of cytokines, and a suboptimal response of antibodies to vaccination.

High levels of IgG1 and IgG3 and low levels of IgG2 and IgG4 have been reported, with normal levels of IgM that decline in adolescence.[23] Although, the majority of these patients develop protective levels of IgG, it has been observed that the specific antibody responses to various immunizations are deficient, so that it is difficult to be certain of the degree of protection provided, and it may be that they cannot maintain sufficient immunity over the long term.[24] The response to antigen vaccines like influenza A, oral polio, acellular pertussis, tetanus, and pneumococcal polysaccharide is low. In a 2012 study, only 27% of patients with DS vaccinated for influenza in a single-dose reached protective antibody levels, as compared with 90% of the general population.[25] The response to vaccines against hepatitis A and B is normal, although the specific doses of IgG may vary.[26]

Given the differences in immune response, some countries suggest complementing the vaccination scheme, but there is still no agreement on criteria. In order to guarantee immunity over time in this population, we agree on the necessity for annual vaccination against influenza, 23-valent pneumococcal polysaccharide vaccine (PPSV23) from the age of 2 years old, and an extra dose of hepatitis B vaccine. Immunizations for chicken pox, meningococcus, and hepatitis A should be included when not part of local vaccination schemes.

Pulmonary hypertension

Patients with DS have a strong predisposition to developing pulmonary hypertension. One important factor in this disorder is the presence of congenital heart disease (CHD), which are found in 50% of patients. CHD with short-circuiting from left to right, especially the complete atrioventricular canal defect, progress most rapidly to pulmonary hypertension.[27-29]

There are also other factors that contribute to this condition, such as pulmonary immaturity, low alveoli population, and delayed development of pulmonary vasculature. Another possible explanation is low levels of nitric oxide and prostacyclin, as well as elevated thromboxane and endothelin in people with DS. It is also necessary to consider common comorbidities in this population, such as sleep apnea, chronic pulmonary aspiration, and recurring pneumonia.[30]

Even though, in most of cases, pulmonary hypertension is transient, studies have identified it as persistent or recurrent in 15% and severe in 12% of cases.[28] The AAP suggests performing an echocardiogram during the prenatal stage and/or the first month of life, and later monitoring based on individual CHD and in patients between 13 to 21 years old, for symptomatology suggestive of aortic or mitral valve disease.[2] Given the increased prevalence of pulmonary hypertension and its complications in DS, we recommend cardiological follow-up at least every two years for early detection and treatment.

Dyslipidemia

Dyslipidemias are an important risk factor for cardiovascular pathologies. Studies have reported that people with DS have less favorable lipid profiles than the general population. These profiles are not positively correlated with obesity, which suggests an underlying genetic explanation. Mortality from ischemic heart disease and

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cerebrovascular disease in the population with DS is up to 4.3 times that of the general population.[31] Early detection and treatment should thus be emphasized in order to avoid complications. The U.S. National Cholesterol Education Program (NCEP) Expert Panel recommends universal initial screening at 9 years old and a second screening from 18 to 21 years old. In populations with risk factors it recommends such screening between 2 and 8 years old.[32,33] A study carried out in our clinic,[34] reported that 54.6% of patients have some type of dyslipidemia, confirming that people with DS should be considered an at-risk population. Therefore, we suggest initial screening at the age of 2 years old and annually thereafter.

Uric acid

Uric acid is a powerful antioxidant. Elevated levels have been reported in patients with DS, as compared with the general population. This may be a compensatory antioxidant effect in response to the ongoing oxidative stress experienced by this population. Some studies have reported elevated levels of allantoin, an oxidation product of uric acid through reactive oxygen species (ROS), which is believed to be the result of overexpression of *SOD1*.[35,36] The increased gene dosage in DS can cause an increase in the adenosine deaminase and adenine phosphoribosyltransferase (APRTase) enzymes that could contribute to elevated levels of uric acid.[37] However, modifiable factors such as obesity, lack of physical activity, and unbalanced diets should also be considered. A positive association has been found between low levels of HDL Cholesteroland hyperuricemia. Regular monitoring of uric acid levels is very important owing to their established relationship with increased risk of diabetes, hypertension, and heart disease.

Studies have reported the incidence of hyperuricemia at 33% in the pediatric population with DS, but this condition has a correlation with age, significantly increasing from the age of 20 years, and appearing primarily in men.[38] Some studies have reported a lowering of uric acid by 19% in patients with DS as the result of daily physical activity of moderate intensity. The use of vitamin C and E supplements attenuate the systemic oxidative damage, although they do not affect the levels of uric acid.[39,40] Studies in the general population suggest nutritional and pharmacological treatment for blood levels of uric acid exceeding 6 mg/dl. We recommend specific testing for this biochemical condition beginning at 2 years old and annually thereafter.

Diabetes mellitus

The prevalence of diabetes mellitus type 1 is 4.2 times greater among people with DS than in the general population. It shows a biphasic pattern,[41,42] with the first peak during the first year of life and the second one around the age of 10 years. Despite the fact that studies have reported that lower levels of insulin are needed for glycemic control, treatment should be individualized to meet the targets recommended by the American Academy of Diabetes (ADA).[43]

Regarding type 2 diabetes mellitus, there are few information at international level.[44] However, there are reasons to believe that patients with DS can present insulin resistance, type 2 diabetes mellitus, and metabolic syndrome more often, among other considerations, due to premature aging, obesity, and sedentary lifestyle.[45] People with DS must be considered an at-risk population for the development of diabetes. We recommend an annual determination of fasting blood sugar and hemoglobin A1c, so that timely action can be taken to prevent complications from this disease.

Vitamin D

In addition to the skeletal functions of vitamin D, studies have shown that it interacts with more than 1250 genes[46] involved in preventing infectious disease, cancer, muscle problems, allergies, and autoimmune disorders. Vitamin D level is defined as deficient at less than 20 ng/dl and sufficient at more than 30ng/dl.[47]A vitamin D supplement of 400 IU/day is recommended during the first 12 months of life.[49] From the age of one year, the recommendation is for a healthy lifestyle with foods rich in vitamin D. The population at risk for deficiency, including those with dark skin, little exposure to sun, sedentary children or those with obesity, and premature infants, should receive an oral supplement.[49]

Vitamin D deficiency is high in children and adolescents,[50] with a greater prevalence in those with DS50 that has been related to muscular hypotonia, low levels of physical activity, poor eating habits, hypogonadism, retarded growth, and thyroid dysfunction.[51]

These data confirm that people with DS should be considered at risk. They should be evaluated for serum levels of 25(OH)D and given supplements to make up for the deficiency,[52] with special attention in patients with comorbidities such as obesity and autoimmune disease.[50]

Autism

Intellectual disability occurs in 12 to 14 out to 10,000 people. In addition to this, neurodevelopmental disorders, such as Autism spectrum disorder (ASD) has been reported in 40% of patients with Down Syndrome (DS).[53] The research in individuals with DS and ASD, shows some areas of subtle differences compared to those with idiopathic ASD. Studies suggest that socialization and empathy are different among children diagnosed with DS and ASD.

Increased rates of stereotyped behaviors and self-injury behaviors are more common in children with ASD coexisting with DS.[54] The features of DS may hinder the recognition of ASD, thus the acknowledgement of this research may represent an opportunity for early diagnosis and intervention, that otherwise is made in late childhood.[55] Investigators recommend this population to be screened as soon as the age of 3 years, with the Modified Checklist for Autism in Toddlers (MCHAT) and the Social Communication Questionnaire (SCQ), which are highly sensitive in identifying children with Down syndrome and autism spectrum disorder.[56]

Conclusion

The purpose of this article is to compile the major findings for people with DS that have not been included in previous health care guidelines. The recommendations presented here can be used by healthcare professionals to provide a better and more effective care with patients. The early detection of some comorbidities can improve prognoses and lower care´s cost for the complications they may cause. Table 2 presents a concise summary of the additional guidelines we propose, with a timeline for each recommendation. Table 3 integrates the guidelines of the AAP and the information compiled by the group of experts in the INP´s Down Syndrome Clinic.

We consider it is vitally important to carry out additional studies to expand our knowledge in this area. There is a need for clinical practice guides compiled with strict methodological rigor that will allow us to improve health care for people with DS and prioritize programs to improve their quality of life.

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Table 2 Additional Health Care Recommendations for Patients with Down Syndrome

Bilirubin	Every neonate in the first 7 days of life
Thyroid function	Repeat thyroid function tests at 15 days of life
Deglutition	Upper gastrointestinal series for suspected deglutition disorders
Additional vaccines	Annual influenza
	PPSV23 at 2 years
	Additional dose of hepatitis B
	Chicken pox, meningococcus, and hepatitis A when not part of local vaccination schemes.
Pulmonary hypertension	Echocardiogram every 2 years
Diabetes mellitus	Annual screening
Lipid profile	Begin at 2 years
	Annual testing thereafter
Uric acid	Annual screening
Vitamin D	400 IU/day in the first year of life
	Evaluate need for supplement thereafter

PPSV23, 23-valent pneumococcal polysaccharide vaccine

Table 3 Health Care Recommendations Proposal

Evaluation	Birth	6 Months	12 Months	2-10 Years	10-18 Years
Genetic	Karyotype and genetic counseling				
Pediatric Exam	At every check-up, evaluate: height, weight, eating habits, deglutition, gastroesophageal reflux, constipation, quality of sleep, sexuality, neurodevelopment, behavior, orofacial and physical therapy				
Cardiology	Echocardiogram and follow-up as indicated			Echocardiogram at least every 2 years	
Thyroid	Neonatal screening Repeat tests of thyroid function at 15 days	Tests of thyroid function	Tests of thyroid function	Annual tests of thyroid function†	
Hematology	Complete blood count Bilirubin in first 7 days	Complete blood count	Complete blood count	Annual complete blood count	
Lipid Profile				Annual screening	
Uric Acid				Annual screening	
Diabetes Screening			Annual screening		
Audiology	Auditory screening	Auditory evoked potential, otoacoustic emission, and tympanometry tests	Auditory evoked potential, otoacoustic emission, and tympanometry tests	Annual screening	
Otorhinolaryngology	Refer in case of problems in audiometric tests or symptomatology				
Sleep Apnea				Polysomnography and evaluation according to symptomatology	
Ophthalmology	Rule out congenital cataract	Evaluation	Annual evaluation		

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Table Continued...

Evaluation	Birth	6 Months	12 Months	2-10 Years	10-18 Years
Dentistry		Evaluation at teething		Dental cleaning and treatment every 6 months	
Orthopedics‡	Rule out hip dysplasia			Evaluation according to symptomatology§	
Vitamin Supplements	Vitamins A, C, D, and E			Supplements according to diet and lifestyle	
Additional Vaccines	Extra dose of hepatitis B¶			Annual influenza PPSV23	
	According to local vaccination scheme. If not included, vaccinate against chicken pox, meningococcus, and hepatitis A.				

PPSV23, 23-valent pneumococcal polysaccharide vaccine

† In case of subclinical hypothyroidism, repeat thyroid function test every 3 months: anti-thyroglobulin antibody, anti-peroxidase, and thyroid ultrasound

‡ Advise parents to avoid excessive neck movement due to atlantoaxial instability

§ Patients doing high-impact exercise should have anteroposterior and lateral x-rays of the cervical column

¶ Consider at 9-12 months, according to immune response

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Conflicts of interest

The authors have no conflicts of interest to disclose.

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