Bari,
7-10 novembre 2013

12° Congresso Nazionale AME
6th Joint Meeting with AACE
Update in Endocrinologia Clinica

SINDROME DI DOWN ED ENDOCRINOPATIE

" DISFUNZIONE TIROIDEA "

DOTT. VINCENZO NOVIZIO

7-10 NOVEMBRE 2013, BARI

DOWN SYNDROME

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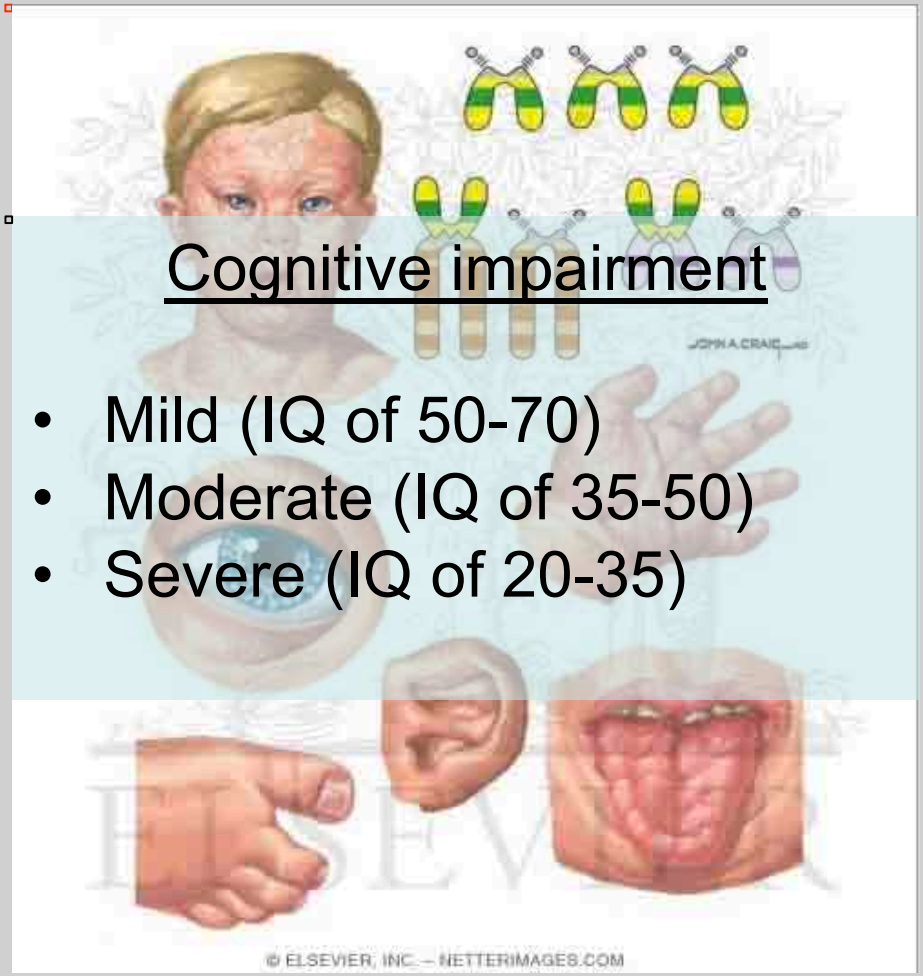
- Approximately 1 in 600 births in the United States.
- Multiple malformations, medical conditions and cognitive impairment because of the presence of extra genetic material from chromosome 21.
  - 47 chromosomes with a free extra chromosome 21 (95%)
  - Unbalanced translocation between chromosome 21 and another acrocentric chromosome, usually chromosome 14 (3-4%)
  - Mosaicism (1-2%)

THE PHENOTYPE IS VARIABLE

MORE COMMON PHYSICAL FINDINGS

- Hypotonia
- Small brachycephalic head
- Epicanthal folds
- Flat nasal bridge
- Upward-slanting palpebral fissures
- Brushfield spots
- Small mouth
- Small ears
- Excessive skin at the nape of the neck
- Single transverse palmar crease
- Short fifth finger with clinodactyly and wide spacing
- Deep plantar groove between the first and second toes



Medical Problems Common in Down Syndrome

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Condition	%
Hearing problems	75
Vision problems	60
Cataracts	15
Refractive errors	50
Obstructive sleep apnea	50–75
Otitis media	50–70
Congenital heart disease	40–50
Hypodontia and delayed dental eruption	23
Gastrointestinal atresias	12
Thyroid disease	4–18
Seizures	1–13
Hematologic problems	
Anemia	3
Iron deficiency	10
Transient myeloproliferative disorder	10
Leukemia	1
Celiac disease	5
Atlantoaxial instability	1–2
Autism	1
Hirschsprung disease	<1

Congenital Hypothyroidism

Mild Hypothyroidism

Autoimmune Hypothyroidism

Graves Disease And Hyperthyroidism

PEDIATRICS Volume 128, Number 2, August 2011

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Congenital Hypothyroidism

Congenital Hypothyroidism

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- General population : 1 : 2.000 – 4.000 newborn infants (F:M = 2:1)
  - Permanent hypothyroidism.
    - Thyroid dysgenesis (aplasia, hypoplasia or ectopia). (The commonest cause)
    - Thyroid hormone biosynthetic defects. (10% of all cases)
    - Iodine deficiency (endemic cretinism).
    - Hypothalamic-pituitary hypothyroidism. (1/60.000 – 1: 140.000)
  - Transient hypothyroidism.
    - TSH binding inhibitory immunoglobulins (1:50.000 births)
    - Exposure to goitrogens (iodides or antithyroid drugs).
    - Transient hypothyroxinemia of prematurity
    - Sick euthyroid syndrome
- Patients with DS : ~ 1: 113

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- An exaggerated response to thyroid-releasing hormone (TRH) stimulation, (implying immaturity of the hypothalamic-pituitary axis)
- Inappropriate TSH secretion
- TSH insensitivity
- Reduced TSH bioactivity,

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Plasma thyrotropin bioactivity in Down's syndrome children with subclinical hypothyroidism.

Konings CH, van Trotsenburg AS, Ris-Stalpers C, Vulsma T, Wiedijk BM, de Vijlder JJ.

The present results demonstrate normal TSH bioactivity in plasma of DS children, indicating that subclinical hypothyroidism in these patients is of primary (thyroidal) origin.

Eur J Endocrinol. 2001 Jan;144(1):1-4.

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Congenital hypothyroidism: increased risk of neonatal morbidity results in delayed treatment.

Fernhoff PM, Brown AL, Elsas LJ.

In a population-based screen of 617,913 infants, primary congenital hypothyroidism (CH) was confirmed in 100 children. 32 of the 100 infants with CH had an additional defect or complication. *In the group with CH the rates of congenital heart disease, non-cardiac malformations, respiratory distress syndrome, and death were higher than in the general population of the same age.* Black infants were less likely than whites to have CH, but were at twice the risk of additional impairment. Infants with CH who had an additional complication were screened (12.7 vs 4.8 days) and treated (32.4 vs 19.7 days) significantly later than those infants with isolated CH. Congenital malformations and neonatal complications should not be reasons for deferring screening for CH.

Lancet. 1987 Feb 28;1(8531):490-1.

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Increased incidence of extrathyroidal congenital malformations in Japanese patients with congenital hypothyroidism and their relationship with Down syndrome and other factors.

Gu YH, Harada S, Kato T, Inomata H, Aoki K, Hirahara F.

Thyroid. 2009 Aug;19(8):869-79

The incidence of ECMs in PCH patients was significantly higher than in the normal population, and ethnic-, sex-, and DS-related differences were observed. Genetic and environmental factors were also identified in PCH patients with ECMs.

Thyroid function in young children with Down syndrome.

Cutler AT, Benezra-Obeiter R, Brink SJ.

Am J Dis Child. 1986 May;140(5):479-83.

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The association of congenital hypothyroidism and congenital gastrointestinal anomalies in Down's syndrome infants.

Jaruratanasirikul S, Patarakijvanich N, Patanapisarnsak C

Congenital hypothyroidism was detected in 17 patients (15.2%); 3 overt congenital hypothyroidism; 6 persistent compensated hypothyroidism; and 8 transient compensated hypothyroidism. Nine of the 20 patients (45%) with congenital gastrointestinal anomalies had congenital hypothyroidism, while 8 out of 92 patients (8.7%) without congenital gastrointestinal anomalies had congenital hypothyroidism. *The odds ratio was 8.59 (95% confidence interval 2.4-31.6; p = 0.0001).*

J Pediatr Endocrinol Metab. 1998 Mar-Apr;11(2):241-6.

Adapted by www.newbornwhocc.org

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- Abnormal values on screening (T4 < 6.5 ug/dL, TSH > 20mu/L) should always be confirmed by a venous sample using age appropriate cut-offs.
- Investigations to determine the etiology such as scintigraphy should be done as soon as the diagnosis is made. If it is not possible, the therapy should be started without delay.
- The initial dose of L-thyroxine should be 10-15µg/ kg/ day with the aim to normalize the T4 level at the earliest. T4 should be kept in the upper half of normal range (10-16 µg/dL) with TSH level suppressed in the normal range.
- Asymptomatic hyperthyrotropinemia should be treated unless the free T4 levels are in upper half of normal range.
- When treatment has been started in an infant with suspected transient hypothyroidism or isolated increase in TSH or borderline values of T4 and TSH, a 6 week trial of putting the child off therapy followed by measuring TSH and T4 levels should be done at 3 years of age.

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PEDIATRICS

OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Health Supervision for Children With Down Syndrome
Marilyn J. Bull and the Committee on Genetics
Pediatrics 2011;128;393; originally published online July 25, 2011;
DOI: 10.1542/peds.2011-1605

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://pediatrics.aappublications.org/content/128/2/393.full.html

American Academy of Pediatrics
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HEALTH SUPERVISION FROM BIRTH TO 1 MONTH: NEWBORN INFANTS

Congenitalhypothyroidism(1%risk). Obtain thyroid-stimulating hormone (TSH) concentration if state newborn screening only measures free thyroxine (T4); congenital hypothyroidism can be missed if only the T4 concentration is obtained in the newborn screening. Many children with Down syndrome have mildly elevated TSH and normal free T4 levels. **Management of children with abnormal thyrotropin or T4 concentrations should be discussed with a pediatric endocrinologist.**

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Lower neonatal screening thyroxine concentrations in down syndrome newborns.

van Trotsenburg AS, Vulsma T, van Santen HM, Cheung W, de Vijlder JJ.

There is an unexplained higher incidence of congenital hypothyroidism (CH) detected by T(4)-based neonatal screening programs and a very high prevalence of (mild) plasma TSH elevation in young children with Down syndrome (DS). To determine whether newborns with DS have decreased blood T(4) concentrations at the time of the neonatal screening, we conducted an observational study in a large and representative cohort of Dutch children with DS born in 1996 and 1997. CH screening results (T(4), TSH, and T(4)-binding globulin concentrations) were analyzed in comparison with clinical information obtained by interviewing the parents and data from the general newborn population and a large control group. The mean T(4) concentration of the studied children with DS (n = 284) was significantly decreased. The individual T(4) concentrations were normally (Gaussian) distributed but shifted to lower concentrations. This could not be explained by prematurity, nonthyroidal illness, or iodine exposure. Mean TSH and T(4)-binding globulin concentrations were significantly increased and normal, respectively. *The decreased T(4) concentration, left-shifted normal distribution, and mildly elevated TSH concentrations point to a mild hypothyroid state in newborns with DS and support the existence of a DS-specific thyroid (regulation) disorder. The question remains whether this contributes to the brain maldevelopment.*

J Clin Endocrinol Metab. 2003 Apr;88(4):1512-5.

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Trisomy 21 causes persistent congenital hypothyroidism presumably of thyroidal origin.

van Trotsenburg AS, Kempers MJ, Endert E, Tijssen JG, de Vijlder JJ, Vulsma T.

These findings suggest that as a group DS infants have a novel type of persistent mild congenital hypothyroidism, presumably of thyroidal origin. The group character suggests a direct relation with the trisomic state of chromosome 21, hypothetically through genomic dosage imbalance of dosage-sensitive genes interfering with thyroid hormone production.

Thyroid. 2006 Jul;16(7):671-80.

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Misdiagnosis of thyroid disorders in down syndrome: time to re-examine the myth?

Prasher V, Haque MS.

There is a reported association between thyroid disorders and Down syndrome, but is this association based on valid and reliable research evidence? We evaluated thyroid function test results of 110 healthy adults with Down syndrome to determine biochemical thyroid status. Approximately two thirds were biochemically euthyroid when assessed by standard reference ranges for the general population. *We believe that there is a need for revalidation of "normal" thyroid function tests parameters when applied to the Down syndrome population and that persons with Down syndrome are possibly being misdiagnosed and inappropriately treated for a nonexistent medical disorder.*

Am J Ment Retard. 2005 Jan;110(1):23-7

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The effect of thyroxine treatment started in the neonatal period on development and growth of two-year-old Down syndrome children: a randomized clinical trial.

van Trotsenburg AS, Vulsma T, van Rozenburg-Marres SL, van Baar AL, Ridder JC, Heymans HS, Tijssen JG, de Vijlder JJ.

The data of our study provide evidence to support the hypothesis that thyroxine treatment may improve development and growth of young Down syndrome children. *Thyroxine treatment should be considered in Down syndrome neonates to maximize their early development and growth.*

J Clin Endocrinol Metab. 2005 Jun;90(6):3304-11.

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ACQUIRED HYPOTHYROIDISM

ACQUIRED HYPOTHYROIDISM

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- Children with DS : 13-54% vs 0,8-1,1 normal population (Fort et al,1984)
- People with DS have an increased risk of developing hypothyroidism at any age.
- Compensated Hypothyroidism or Clinical Hypothyroidism
- A person with DS every 12 presents Compensated Hypothyroidism or Clinical Hypothyroidism (Rasore-Quartino and Cominetti, 1994)

- Constipation,
- Dry skin,
- Muscle weakness,
- Fatigue,
- Weight gain

- HEALTH SUPERVISION FROM BIRTH TO 1 MONTH: NEWBORN INFANTS
  - Congenitalhypothyroidism(1%risk). Obtain thyroid-stimulating hormone (TSH) concentration if state newborn screening only measures free thyroxine (T4); congenital hypothyroidism can be missed if only the T4 concentration is obtained in the newborn screening. Many children with Down syndrome have mildly elevated TSH and normal free T4 levels. Management of children with abnormal thyrotropin or T4 concentrations should be discussed with a pediatric endocrinologist.
- HEALTH SUPERVISION FROM 1 MONTH TO 1 YEAR: INFANCY
  - Verify results of newborn thyroid- function screen if not previously performed. Because of increased risk of acquired thyroid disease, *repeat measurement of TSH at 6 and 12 months of age and then annually.*
- HEALTH SUPERVISION FROM 1 TO 5 YEARS: EARLY CHILDHOOD
  - *Measure TSH annually* or sooner if child has symptoms that could be related to thyroid dysfunction.
- HEALTH SUPERVISION FROM 5 TO 13 YEARS: LATE CHILDHOOD
  - Measure TSH annually; the risk of hypothyroidism increases with age.

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Prevalence of abnormal thyroid function tests in a Down's syndrome population.

Rooney S, Walsh E.

As thyroid function has been documented to be of a higher prevalence in individuals with Down's syndrome, a study was set up to assess the thyroid status of these individuals. Thyroid function tests (T.F.T.s) were initially reviewed on 100 individuals with Down's syndrome in the community and on 36 individuals who were residentially based. Abnormal T.F.T.s were then reviewed 3 yr later. In total sample of 136, initially 13 percent [n = 18] of individuals with Down's syndrome had abnormal T.F.T.s, 5 percent [n = 7] were established cases of thyroid disease and 8 percent [n = 11] were newly identified cases who had abnormal T.F.T.s. Three yr later 6.5 percent [n = 9] of the group who had had abnormal T.F.T.s continued to have abnormal T.F.T.s, 5 percent [n = 7] had thyroid disease and 1.5 percent [n = 2] still had biochemical evidence of thyroid dysfunction. There was a statistically significant increase in abnormal T.F.T.s in the residential sample compared to the community sample on both occasions. The incidence of thyroid dysfunction has been found to increase with age, particularly over the age of 40, however in this study the majority were under the age of 40 with an age range between 28.3 yr and 33.8 yr. The results in this study, coupled with the variability of T.F.T.s over time, highlights the need for regular monitoring of the thyroid status of individuals with Down's syndrome.

Ir J Med Sci. 1997 Apr-Jun;166(2):80-2.

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Autoimmune thyroiditis associated with mild "subclinical" hypothyroidism in adults with Down syndrome: a comparison of patients with and without manifestations of Alzheimer disease.

Percy ME, Dalton AJ, Markovic VD, Crapper McLachlan DR, Gera E, Hummel JT, Rusk AC, Somerville MJ, Andrews DF, Walfish PG.

Serum tests of thyroid function were compared in Down syndrome (DS) patients with and without manifestations of Alzheimer disease (AD). Relative to control individuals, DS patients had, overall, lower mean total T4 (P = 0.070) and T3f (P = 0.015), higher T3U (P = 0.013) and TSH (P = 0.020), no difference in free T4, and higher thyroid antithyroglobulin (ATA) (P = 0.033) and antimicrosomal autoantibody (AMA) titres (P = 0.0097). Similar trends were apparent in DS males and females, and in DS patients off all drugs. In an analysis of case/control pairs with corrections for age and sex, DS patients with AD manifestations (n = 9) had significantly lower T3 (P = 0.029) and higher AMA (P = 0.043) than paired control individuals, whereas DS patients without AD manifestations (n = 20) had significantly lower T3 (P = 0.013) but higher ATA (P = 0.0065). T3 was significantly lower in the DS patients with AD manifestations than in the unaffected (P = 0.0013). These data suggest that autoimmune thyroiditis associated with a mild "subclinical" form of hypothyroidism is common in adult DS patients and more pronounced in patients with AD manifestations than in those without. *This "subclinical" hypothyroidism may contribute to cognitive deficits in ageing DS patients.*

Am J Med Genet. 1990 Jun;36(2):148-54

Growth studies in infants and children with Down's syndrome and elevated levels of thyrotropin.

Sharav T, Collins RM Jr, Baab PJ.

A retrospective survey of 147 patients with Down's syndrome (age range, 4 months to 27 years) showed that 60% had a thyrotropin (TSH) level higher than 5.7 mU/L in the presence of high or normal thyroxine levels. The remaining 40% of the group had low to normal TSH values. High TSH levels were predominant in patients under 4 years of age (94 children), ie, during the phase of active growth, and showed a declining trend with increasing age. *All 94 infants had delayed growth of all parameters including head circumference, height, and weight, as compared with normal infants, and growth was particularly retarded in patients with TSH levels greater than 5.7 mU/L.* Thyroid dysfunction, expressed as a high TSH concentration, is associated with growth retardation in children with Down's syndrome who are younger than 4 years.

Am J Dis Child. 1988 Dec;142(12):1302-6

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A five-year longitudinal study of thyroid function in children with Down syndrome.

Selikowitz M

The thyroid function and health status of 101 children with Down syndrome were assessed annually for five years. One child had congenital hypothyroidism at entry to the study. During the study period, eight more developed compensated hypothyroidism. Five of 10 children with compensated hypothyroidism still had the condition at the end of the study, it resolved spontaneously in four and one child developed uncompensated hypothyroidism. *There were no significant differences in growth and development between those with compensated hypothyroidism and those with normal thyroid function.* Two children developed transient rises in thyroxine, associated with elevations in thyroid-stimulating hormone (TSH). A large proportion of thyroid dysfunction in children with Down syndrome is transient and may be related to inappropriate secretion of TSH or thyroid insensitivity to TSH, rather than to auto-immune thyroiditis.

Dev Med Child Neurol. 1993 May;35(5):396-401.

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TSH neurosecretory dysfunction (TSH-nd) in Down syndrome (DS): low risk of progression to Hashimoto's thyroiditis.

Faria CD, Ribeiro S, Kochi C, Silva AP, Ribeiro BN, Marçal LT, Santos FH, Eduardo CP, Monte O, Longui CA.

INTRODUCTION:
Patients with Down syndrome (DS) often have elevated TSH (hypothalamic origin), which is called TSH neurosecretory dysfunction (TSH-nd). In these cases, there is slight elevation in TSH (5-15 µUI/mL), with normal free T4 and negative thyroid antibodies (AB).
OBJECTIVE:
To recognize the risk of progression to Hashimoto's thyroiditis (HT).
SUBJECTS AND METHODS:
We retrospectively analyzed 40 DS patients (mean age = 4.5 years), followed up for 6.8 years.
RESULTS:
HT was diagnosed in 9/40 patients, three early in monitoring, and six during evolution. In 31/40 patients, TSH-nd diagnosis remained unchanged over the years, with maximum TSH values ranging from 5 to 15 µUI/mL. In this group, free T4 also remained normal and AB were negative. There was a significant TSH reduction ($p = 0.017$), and normal TSH concentrations (< 5.0 µUI/mL) were observed in 29/31 patients, in at least one moment. No patient had TSH > 15 µUI/mL.
CONCLUSION:
DS patients with TSH-nd present low risk of progression to HT (10% for females and 6% for males).

Arq Bras Endocrinol Metabol. 2011 Nov;55(8):628-31

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Short-term efficacy of thyroid hormone supplementation for patients with Down syndrome and low-borderline thyroid function.

Tirosh E, Taub Y, Scher A, Jaffe M, Hochberg Z.

The thyroid function of 44 subjects with Down syndrome who were between 2 and 51 years of age was assessed. Three patients (7%) had hypothyroidism, and in 2 of them high titers of antimicrosomal antibody were detected. Seven additional subjects (16%) had low-borderline thyroid function, 6 with elevated thyroid stimulating hormone. These 7 subjects constituted the cohort for an evaluation of the short-term benefits of thyroid hormone supplementation in the low-borderline thyroid functional state*. A double-blind crossover drug placebo trial failed to document any cognitive, social, response time, or physical changes attributable to the 8- to 14-week drug treatment period compared to an untreated matched control group*. Results provided no evidence for the efficacy of short-term thyroid hormone therapy for this population.

Am J Ment Retard. 1989 May;93(6):652-6

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Zinc affects the metabolism of thyroid hormones in children with Down's syndrome: normalization of thyroid stimulating hormone and of reversal triiodothyronine plasmic levels by dietary zinc supplementation.

Licastro F, Mocchegiani E, Zannotti M, Arena G, Masi M, Fabris N.

Levels of circulating thyroid stimulating hormone (TSH), tetraiodothyronine (T4), 3,5,3'-triiodothyronine (T3), and 3,3',5' triiodothyronine (reversal T3 or rT3) were measured in 25 children with trisomy of chromosome 21, also known as Down's syndrome (DS), and in 14 normal children. In subjects with DS TSH levels were increased, while plasmic levels of rT3 were decreased. No alteration in T3 and T4 levels was observed. Before zinc supplementation, plasmic levels of zinc and thymulin, a zinc dependent thymic hormone, were significantly decreased in DS children. *After four months of dietary supplementation with zinc sulphate, a normalization of plasmic zinc, thymulin and TSH levels was observed.* Plasmic levels of rT3 significantly increased, and after zinc treatment no difference was detectable between DS children and normal children. Clinical evaluation of the health status of DS children showed that zinc supplementation decreased the incidence of infectious diseases and improved school attendance. Thus, the increased efficiency of the immune system and the normalization of some endocrine parameters by zinc supplementation suggests that zinc deficiency may play a crucial role in some of the pathological manifestations associated with the syndrome, such as infections and malfunctioning of the thyroid gland.

Int J Neurosci. 1992 Jul-Aug;65(1-4):259-68.

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Effect of zinc supplementation on thyroid hormone metabolism of adolescents with Down syndrome.

Marreiro Ddo N, de Sousa AF, Nogueira Ndo N, Oliveira FE.

Studies have evidenced that zinc metabolism is altered in the presence of Down syndrome, and zinc seems to have a relationship with the metabolic alterations usually present in this syndrome. In this work, the effect of zinc supplementation on thyroid hormone metabolism was evaluated in adolescents with Down syndrome. A prospective study was carried out on 16 adolescents with Down syndrome (age: 10-19 years) who were randomized for treatment with 30 mg zinc daily for 4 weeks. Diet evaluation was accomplished y using a 3-day dietary record, and the analysis was performed by the NutWin program, version 1.5. Anthropometric measurements were performed for evaluation of body composition. The Zn-related nutritional status of the groups was evaluated by means of zinc concentration determinations in plasma and erythrocytes using the method of atomic absorption spectroscopy, and the thyroid hormone was obtained by radioimmunoassay. The diet of patients with Down syndrome, before and after the intervention presented reduced energy level and adequate zinc concentrations. Mean plasma zinc values were 59.2 +/- 13.2 and 71.0 +/- 21.9 microg/dL before and after the intervention, respectively. Erythrocyte concentrations of the mineral before supplementation, instead, were 51.5 microg/dL +/- 11.1 microg Zn/gHb, and at the end of the experiment, they were 42.9 +/- 8/5 microg Zn/gHb, with a significant statistical difference ($p < 0.05$). Serum concentrations of T(4) hormone before and after zinc supplementation were 1.26 +/- 0.20 and 1.54 +/- 0.63 pg/mL, respectively. Mean T(3) values before intervention were 2.47 +/- 037 pg/mL and, after supplementation, 2.25 +/- 0.67 pg/mL, without significant statistical difference ($p > 0.05$). *Intervention with zinc showed to be effective in the stabilization of the concentrations of this mineral in plasma and erythrocytes, but had no influence on the metabolism of thyroid hormones.*

Biol Trace Elem Res. 2009 Summer;129(1-3):20-7.

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AUTOIMMUNE HYPOTHYROIDISM

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Current dilemmas in Down syndrome clinical care: celiac disease, thyroid disorders, and atlanto-axial instability.

Cohen WI.

Prevalence of celiac disease in this population has been reported to be as high as 5% to 10%

Am J Med Genet C Semin Med Genet. 2006 Aug 15;142C(3):141-8.

Thyroid autoantibodies : 13-34%

Hypothyroidism : 3-54%

Increased incidence and prevalence of diabetes mellitus in Down's syndrome

J C VAN GOOR, G MASSA, and R HIRASING

The risk of type 1 diabetes is 3 times higher than that in the general pediatric population

Arch Dis Child. 1997 August; 77(2): 183.

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Thyroid dysfunction in Down's syndrome: relation to age and thyroid autoimmunity.

Karlsson B, Gustafsson J, Hedov G, Ivarsson SA, Annerén G.

To study longitudinally thyroid function in patients with Down's syndrome in Uppsala county (85 patients) up to the age of 25 years.

Observational study based on yearly follow up in a children's clinic. Thyroid function tests were performed at each visit to the clinic.

Hypothyroidism was found in 30 and hyperthyroidism was found in two of the 85 patients. No sex difference was seen. Half of the patients with hypothyroidism acquired the condition before the age of 8 years, but only one of them displayed thyroid autoantibodies at diagnosis. Most patients who developed hypothyroidism after this age had thyroid autoantibodies. In the prepubertal patients with hypothyroidism, growth velocity was lower during the year before the start of thyroxine treatment than during the year after treatment began; it was also lower than that of sex and age matched euthyroidic children with Down's syndrome.

Thyroid dysfunction in patients with Down's syndrome is common in childhood. Consequently, annual screening is important. *Autoimmune thyroid disease is uncommon in young children with Down's syndrome but is common after 8 years of age*.

Arch Dis Child. 1998 Sep;79(3):242-5

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Susceptibility to autoimmune thyroiditis in Down's syndrome is associated with the major histocompatibility class II DQA 0301 allele.

Nicholson LB, Wong FS, Ewins DL, Butler J, Holland A, Demaine AG, McGregor AM.

In contrast to Hashimoto's thyroiditis and atrophic thyroiditis, there is a strong association between class II genotypes and hypothyroid autoimmune disease in Down's syndrome. This implies a role for a gene or genes on chromosome 21 in the development of autoimmune thyroid disease.

Clin Endocrinol (Oxf). 1994 Sep;41(3):381-3.

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Online Mendelian inheritance in man, OMIM. Johns Hopkins University, Baltimore (MD). MIM Number: 240300: 1/27/12:

World Wide Web URL: Available at*: http://omim.org/. Accessed July 19, 2012.*

AIRE gene (AutoImmune Regulator) : The gene responsible for autoimmune polyendocrinopathy syndrome type I (ASP-1)

Location	Phenotype	Phenotype MIM number
21q22.3	Autoimmune polyendocrinopathy syndrome , type I, with or without reversible metaphyseal dysplasia	240300

Primary hypoparathyroidism, adrenocortical failure, and mucocutaneous candidiasis,

2% to 13% of affected patients have been reported to also have autoimmune thyroid disease.

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Resistance to thyroid hormone and Down syndrome: coincidental association or genetic linkage?

Fernández-García JC, López-Medina JA, Berchid-Debdi M, Tinahones FJ.

Thyroid. 2012 Sep;22(9):973-4.

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Autoantibodies linked to autoimmune polyendocrine syndrome type I are prevalent in Down syndrome.

Söderbergh A, Gustafsson J, Ekwall O, Hallgren A, Nilsson T, Kämpe O, Rorsman F, Annerén G.

Patients with Down syndrome are prone to autoimmune diseases which also occur in the recessive disease autoimmune polyendocrine syndrome type I (APS I). Since this disease is caused by mutations in the gene AIRE on chromosome 21, one might speculate that altered expression of AIRE contributes to autoimmune disease in Down syndrome.

Seven of 48 patients had elevated titres of autoantibodies: one against 21-hydroxylase, three against aromatic L-amino acid decarboxylase, one against cytochrome P4501A2, one against glutamic acid decarboxylase 65 and one against tyrosine phosphatase IA-2. None of the patients had clinical or laboratory signs of disease coupled to the respective autoantibody.

Four patients with Down syndrome had autoantibodies hitherto regarded as unique for APS I, which may suggest a dysregulation of AIRE.

Acta Paediatr. 2006 Dec;95(12):1657-60

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GRAVES DISEASE AND HYPERTHYROIDISM

GRAVES DISEASE AND HYPERTHYROIDISM

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- General population : 1 : 5.000 children (0,02%).

  Female predominance

- Patients with DS : 6,55 in 1000 (0,66%)
  - Occours predominantly between late childhood and early adulthood
  - Does not seem to have an increased risk for females.

Table 3
Comparison of treatment recommendations for Graves disease in DS

Authors	n	Initial Treatment	Relapse Rate After Withdrawal of Medical Treatment (%)	Recommended Initial Treatment
Goday-Arno et al[56]	12	Carbimazole	100	I-123 ablation
DeLuca et al[57]	28	Methimazole	7.1	Methimazole
Bhowmick and Grubb[58]	5	PTU	N/A	PTU

Nelson textbook of pediatrics. 18th edition. Philadelphia: Saunders Elsevier; 2007. p. 2333.

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Graves' disease in a Down's syndrome patient responds well to radioiodine rather than antithyroid drugs.

Damle N, Das K, Bal C.

Children with DS and hyperthyroidism should always be treated with radioactive I-131 ablation because of frequent failure to go into remission while on carbimazole for up to 2 years and repeated relapses when taken off carbimazole.

J Pediatr Endocrinol Metab. 2011;24(7-8):611

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Peculiarities of Graves' disease in children and adolescents with Down's syndrome.

De Luca F, Corrias A, Salerno M, Wasniewska M, Gastaldi R, Cassio A, Mussa A, Aversa T, Radetti G, Arrigo T.

Female prevalence (50 vs 81.6%; chi(2)=12.0, P<0.0005) and average age at GD presentation (9.9+/-4.4 vs 11.5+/-3.5 years, P<0.05) were significantly lower in DS group than in controls. Clinical responsiveness to methimazole therapy was significantly better in DS patients, as demonstrated by both the *lower relapse rates after the first cycle withdrawal (7.1 vs 31.2%; chi(2)=7.4, P<0.005) and the higher persistent remission rates after definitive therapy withdrawal (46.4 vs 26.7%; chi(2)=4.1, P<0.05)*. Moreover, in DS group, no patients needed surgery or radioiodine ablation, whereas non-pharmacological treatment was necessary in 11% of controls (chi(2)=3.8, P<0.05). Antecedents of Hashimoto's thyroiditis (HT) were documented in 21.4% of DS patients and in 3.7% of controls (chi(2)=10.4, P<0.005). Association with other autoimmune diseases was detected in 32.1% of DS cases and in 12.8% of controls (chi(2)=5.94, P<0.025).

Eur J Endocrinol. 2010 Mar;162(3):591-5.

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Graves' disease in a Down's syndrome patient.

Bhat MH, Saba S, Ahmed I, Kamili MM, Khan SA.

- The treatment should be individualized and all available options considered when recommending treatment of hyperthyroidism in patients with DS.
- Each treatment modality has its own risks and benefits; medical treatment may be complicated by poor compliance, whereas radioactive iodine may increase the risk of nonthyroidal malignancy
- Surgery is invasive, but may be indicated in refractory cases of Graves disease or when radioactive iodine is not indicated or desired by the patient and family.

J Pediatr Endocrinol Metab. 2010 Nov;23(11):1181-3.

CONCLUSIONS

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- Thyroid dysfunction occurs in 4% to 18% of children with DS and can occur as early as birth.

Congenital Hypothyroidism…..... 1:113 (vs 1:2.000-4.000)
Subclinical Hypothyroidism……... 25-35%
Autoimmune Hypothyroidism…… 13-34%
Graves Disease …….. 0,66% (vs 0,02%)

- The optimal timing and method for thyroid screening in children with DS remain controversial.
- Consensus is needed to establish working definitions of euthyroidism, subclinical hypothyroidism and mild hypothyroidism in all infants, but especially in those with DS.
- What is the best course of treatment for subclinical hypothyroidism ?

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Thyroid dysfunction in children with Down syndrome: a literature review.

King K, O'Gorman C, Gallagher S.

In conclusion, *more evidence is required regarding the optimal course of treatment for subclinical hypothyroidism*.

Such evidence may be best obtained by conducting a prospective randomized control trial.

Ir J Med Sci. 2013 Aug 10.

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THANKS FOR YOUR ATTENTION