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Original Article

Thyroid dysfunction in Down syndrome

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Abstract
Background: Down syndrome is associated with various forms of thyroid dysfunction, hypothyroidism being the most common. The additive effects of both co-morbid conditions lead to further amplification of the clinical problems in these children with Down syndrome.
Objective: The purpose of this prospective study was to know the prevalence of thyroid dysfunction in Down Syndrome children below the age of 14 years and to correlate the features of Down Syndrome with those of thyroid dysfunction.
Methods: In all 32 Down syndrome children were grouped as euthyroid, compensated and uncompensated hypothyroidism on the basis of their T3, T4 and TSH levels and the features of were compared using the student's t-test.
Results: Hypothyroidism was seen in 5 out of 32 cases (15.6%) of which 1 (3.1%) had uncompensated while the other 4 (12.5%) had a compensated hypothyroidism. Hyperthyroidism was not observed in any of the cases. The prevalence of hypothyroidism of 16.7% on the age group 0 –1 year could well be a reflection of congenital hypothyroidism while 20% prevalence in the age group 9 – 12 could imply acquired hypothyroidism. The mean values of the developmental quotient (D.Q.) and the Rao's index in Down syndrome cases with hypothyroidism was 49 ±5.1 and 0.15 ± 0.06 respectively while that of euthyroid Down syndrome patients were 52 ± 5.54 and 0.17 ± 0.04 respectively ('p' value > 0.05), the differences though obvious yet not statistically significant.
Conclusion: It thus seems necessary to screen all Down syndrome children for thyroid dysfunction.

Key words: Down syndrome, hypothyroidism

Down syndrome is the most common significant chromosomal anomaly in live births with an incidence of 1:800 live births. Down syndrome consists of a constellation of clinical signs and symptoms as well as biochemical, metabolic and endocrine dysfunctions with one common denominator in the form of three copies of the q22 band on long arm of chromosome 21.

The various forms of thyroid dysfunction in Down syndrome may be congenital or acquired, compensated or uncompensated hypothyroidism, transient hypo or hyper–thyroidism, or even persistent hypothyroidism. A review of literature shows that 3% to 54% of Downs' individuals have biochemical evidence of hypothyroidism[1, 2, 3].

The clinical symptoms and signs of both Downs syndrome and hypothyroidism are overlapping to some extent e.g. hypotonia, lethargy, dullness, mental retardation, growth failure, prolonged neonatal jaundice, delayed closure fontanellae, macroglossia, obesity etc. The presence of undetected hypothyroidism in a Downs' child could compound the problems in an already compromised situation, the same being true of other forms of thyroid dysfunction in Down syndrome. Hence the need to study the thyroid dysfunctions in a Down syndrome child so that one can intervene early and decrease the morbidity and mortality in such cases. The aim of the study was to estimate the prevalence of hypo/hyper-thyroidism in Downs' children and to test if there was significant difference in the growth and development in Downs' children with thyroid dysfunction.

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Materials and methods

The study was carried out on 32 children who met the phenotypic criteria for establishing the diagnosis of Down syndrome at the Paediatrics Department, Pandit Bhagwat Dayal Sharma Postgraduate Institute of Medical Sciences, Rohtak, Haryana, India, within the period, starting from May 15th, 2001 to Oct 15th, 2002. The eligibility criteria of the study included patients diagnosed to be cases of Down syndrome as suggested by mental retardation, brachycephaly, upslanted palpabral fissures, epicanthal fold, single simian crease, clinodactyly, short stature, hypotonia, macroglossia, wide space between big and 2nd toe, dermatoglyphics (ulnar loops, distal triradii, single simian crease). A detailed record of the above was be made in all patients of Down syndrome. Patients who already were on thyroxine or antithyroid therapy were excluded. Down syndrome patients in whom there was a family history of goitre, thyrotoxicosis, myxoedema or Hashimoto's thyroiditis were also excluded.

A detailed record of the clinical signs and symptoms of hypothyroidism or hyperthyroidism, if any, were made and the following investigations carried out in the subjects included: X-ray long bones for bone age, X-ray chest, Complete haemogram, Blood sugar, Serum cholesterol, Ultrasound of thyroid, Serum Triiodothyronine (T_3), Thyroxine (T_4), Thyroid Stimulating Hormone (TSH) levels. The technique of radioimmunoassay was adopted for the estimation of the thyroid hormones and thyrotropin. On the basis of above investigations patients were grouped as euthyroid, hyperthyroid, compensated hypothyroid or uncompensated hypothyroid. Data was analysed using the student's "t" test.

Results

Out of the 32 Down syndrome children included in the study, 23 (71.88%) were male while 9 (28.12%) were female. The mean age was 3.31 ± 3.19 years. The highest number of children 12 (37.5%) was in the 0 – 1 year age group. The youngest subject was 1 month old and the oldest was 12 years old. The mean weight was 13.5 ± 11.5 Kilograms. The mean height was 80.9 ± 28.8 centimetres. The mean mid arm circumference was 14.4 ± 4.1 cms. The mean head circumference was found to be 44.0 ± 5.8 cms. The individual values were compared with the standard growth charts for Down syndrome children provided by Cronk C et al.[4] The individual anthropometric measurements were all within the 25th and 75th percentiles for the matched age and sex.

Among the features of Down syndrome mental retardation, short stature and upslanted palpabral fissures were present in all the cases. The other common features included brachycephaly and epicanthal folds present in 84.4% and 90.6% respectively. Clinodactyly (65.5%), hypotonia (50%) and sandal gap between the big and the 2nd toe (50%) were also common. Among the dermatoglyphic patterns single simian crease though characteristic of Down syndrome was seen in 68.8% of the cases. It was the most common feature of the dermatoglyphic patterns observed. This was followed by the presence of distal triradius (53.1%). Ulnar loops were present in all 10 fingers in 15.6 % of the cases. 'H' Pattern in the interdigital area was seen in 12.5% of the cases.

A detailed record of the probable clinical signs and symptoms of hypo and hyper-thyroidism was simultaneously recorded and the following observations were made. Among the features possibly attributable to hypothyroidism mental retardation and growth failure were universally present in all the cases. Hypotonia (50%) lethargy (53.1%) dullness (50%) macroglossia (65.5%) and decreased appetite (57.5%) were notably present. Two (6.25%) of the cases gave a history of prolonged neonatal jaundice while delayed closure of fontanellae was found in 5 (15.6%). The classical cold intolerance and delayed relaxing reflexes were not observed in any of the subjects. None of the children had any true clinical evidence of hyperthyroidism. Tachycardia and cardiomegaly was present in 4 and 5 cases (12.5% and 18.5% respectively) and was present in those cases that had associated congenital heart defects and bronchopneumonia. None of the cases had associated congenital gastrointestinal anomalies.

The mean value of haemoglobin levels in the cases was 9.9 ± 2.3 g/dL. The mean levels of blood sugar and serum cholesterol were 90.1 ± 13.6 mg /dL and 100.6 ± 26.1 mg/dL respectively. The individual values were all within the physiological limits. The bone age estimated from the skeletal radiographs was largely same as the chronological age as reported by the radiologists. The ultrasonographic examination of the thyroid gland in all the cases was also normal. A plain chest radiograph of each child was taken and cardiomegaly was observed in 5 (18.75%) all of whom were aged less than 5 yrs. These children had evidence of cardiac defects later determined to be ventricular septal defects.

The mean T3, T4 and TSH values were 138.0 ± 41.2 ng/dL, 8.7 ± 2.4 μg/dL and 5.4 ± 2.9 mU/L. Five

(18.75%) were found to have hypothyroidism out of which 4 (12.5%) were found to have compensated hypothyroidism i.e. raised TSH values in the face of normal T4 levels, while only 1 (3.1%) was detected to be having uncompensated hypothyroidism. Of the five found to have hypothyroidism 3 (9.4%) were male and 2 (6.25%) were female. In the rest 27 (84.4%) children, including 20 (62.5%) boys and 7 (31.9%) girls the values of the thyroid hormones and thyrotropin levels were well within the physiological limits (Table 1). Hypothyroidism was observed in 16.7% in the age group 0 – 1 year, while in the age group 1 – 3 years and 9 – 12 years the prevalence was 20% each. No thyroid dysfunction was observed in the age groups 3 – 6 years and 6 – 9 years (Table 2).

The mean values of the developmental quotient (D.Q) and the Rao's index (weight/height^2) in Down syndrome cases with hypothyroidism was 49 ±5.1 and 0.15 ± 0.06 respectively while that of euthyroid Down syndrome patients were 52 ± 5.54 and 0.17 ± 0.04 respectively ('p' value > 0.05).

Table 1: Distribution of the thyroid status in the Downs' subjects.

S.N.	Category	Down syndrome pts (%)	Euthyroid (%)	Compensated hypothyroid (%)	Uncompensated hypothyroid (%)	Hyperthyroid (%)
1)	Total no.	32 (100)	27 (84.4)	4 (12.5)	1 (3.13)	0
2)	Male	23 (71.8)	20(62.5)	2 (6.25)	1 (3.13)	0
3)	Female	9 (21.2)	7 (21.9)	2 (6.25)	0	0

Table 2: Age-wise distribution of the thyroid status in Downs' subjects.

S.N.	age groups(yrs)	No. of cases	hypothyroid	%	euthyroid	%
1	0-1	12	2	16.7	10	83.3
2	1-3	10	2	20	8	80
3	3-6	3	0	0	3	100
4	6-9	2	0	0	2	100
5	9-12	5	1	20	4	80

Discussion

Among the features possibly attributable to hypothyroidism, mental retardation and growth failure were universally present in all the subjects. The mean D.Q. in the Down syndrome children with hypothyroidism was 49.5 ± 5.5, while that in the Down syndrome children without evidence of thyroid dysfunction was 52 ± 5.54. The difference though obvious was not statistically significant. Intelligence quotient (I.Q.) was estimated in children above 3 years age, and the mean I.Q. was found to be 47.5 ± 6.2. The presence of lower D.Q. or I.Q. is characteristic of both Down syndrome and hypothyroidism. Mental retardation is universally present in patients of Down syndrome as is observed in this study also. The I.Q. in Down syndrome cases ranges from 25 – 70 with higher values (50 – 59) in younger subjects than in the older subjects (25 – 49) who are at an increased risk for dementia of the Alzheimer's type of a presenile onset due to the development of senile plaques and non-degradable neurofibrillary tangles in the brain (Conolly, 1978 and Carr, 1988).[5, 6]. The cause of mental retardation in Down syndrome children could be due to improper switching over of the foetal forms of insulin-like growth factors (IGF's) to the adult forms[7]. These IGF's are produced endogenously in the brain, both growing and mature, and are responsible for brain growth and myelination and synaptogenesis independent of the action of growth hormone. Hypothyroidism causes delay in synaptogenesis and myelination as well as decreases the brain growth potential, as it is the hormone responsible for maintaining the basic metabolism of all the tissues. The individual anthropometric measurements were all within the 25th and 75th percentiles for the matched age and sex. The Rao's index though low for the Down syndrome cases with hypothyroidism than the

euthyroid, was not statistically significant. Mark Selikowitz[8] in his 5-year longitudinal study of Down syndrome patients also did not discover any statistically different growth and developmental rates between euthyroid and hypothyroid Down syndrome children. Similar findings were noted by van Trotsenburg AS et al (2005)[9] regarding mental development though the physical parameters in hypothyroid Down syndrome patients with thyroxin supplementation were statistically different from the control group. As mental and physical retardation are common denominator to both Down syndrome and hypothyroidism, and, both the conditions are known to co-exist it becomes important to screen the Down syndrome children for hypothyroidism because the co-existence of both the conditions would lead to further developmental delay.

The prevalence of biochemical evidence of hypothyroidism has been variously reported by various authors as 1.8%[10], 4%[11], 6%[12], 8%[13], 17%[14], 30%[2] and 54%[3]. In another study by Thorpe–Beeston et al [15] umbilical cord blood venous sample by cordoscentesis from seventy five foetuses with congenital anomalies showed that all five with Down syndrome had elevated TSH levels while most of the others had normal TSH levels. The prevalence of 16.7% in the age group 0 – 1 year in the present study could well be taken as a reflection of the prevalence of congenital hypothyroidism. van Trotsenburg AS et al (2003)[16] observed that decreased T_4 concentration, left-shifted normal distribution, and mildly elevated TSH concentrations point to a mild hypothyroid state in newborns with Down syndrome could support the existence of a Down syndrome-specific thyroid (regulation) disorder.

Transient hypothyroidism is the most common form of thyroid dysfunction observed in Down syndrome patients. Mark Selikowitz[8] had observed in his longitudinal study that 40% of these cases of compensated hypothyroidism resolved spontaneously. Gibson PA et al (2005)[17] observed that 47% of subclinical hypothyroid Down syndrome patients were subsequently found to have normal TSH levels after a gap of four to six years.

The acquired form of hypothyroidism is usually associated with thyroid antibodies of different types and is more common in children above 8 years. Hypothyroidism was observed in 20% of the cases between 9 – 12 years. Thyroid antibodies were, however, not estimated in the present study as it was not included in the study protocol.

There is a wide variation in the data regarding the prevalence of thyroid dysfunction among Down syndrome patients. However what is clear from the review of literature available till date is that the incidence of congenital hypothyroidism in Down syndrome cases is definitely higher (30 times) than that in the general population. The proposed mechanism for the transient nature of congenital hypothyroidism in Down syndrome could be due to the delayed maturation of the hypothalamic pituitary axis which in turn could be due to delayed switching over of the somatomedines from the foetal to the adult forms. TSH receptor or their signalling proteins (Gsά) could be another possible mechanism but Tonacchera M et al (2003)[18] could not find any inactivating mutations of the corresponding genes in their study of 12 patients. Autoimmune thyroiditis leading to hypothyroidism occurring in young children with Down syndrome has been well recognized, substantiated clinically by association of other autoimmune disease like alopecia areata and biochemically by finding anti-microsomal and anti–thyroglobulin antibodies in patients with Down syndrome. Many thymus dependent immunological abnormalities described in Down syndrome may help to explain the occurrence at a very young age of autoimmune thyroiditis which is thought to be due to a genetically determined, organ specific defect in suppressor T-lymphocytes.

Hyperthyroidism was not observed in any of the cases included in the study, though a few anecdotal reports of hyperthyroidism in Down syndrome patients have been presented by Pozzan GB et al [19] (2%) and Friedman DL et al [20] (1.4%). The Hyperthyroidism observed in rare instances is either attributed to early changes in autoimmune thyroiditis or a manifestation of a self-limiting process unrelated to any autoimmune disorder, a transient hypothalamic- pituitary dysfunction rather than some thyroid disease. Goitre is not a particular feature of thyroid disease in Down syndrome. None of the cases had any clinical or radiological evidence of enlarged thyroid gland.

It is not known how often thyroid function tests should be done in patients with Down syndrome or whether TRH stimulation tests would help to differentiate subsets of patients with Down syndrome who are at future risk for thyroid disorders. Based on their observation of a 19 % prevalence of hypothyroidism in Down syndrome patients and intensive screening process in their study Mitchell C et al[21] recommended a schedule of screening Down syndrome patients at 6 weeks 4, 10,

16, 24 months and annually thereafter. Tuyuz B et al (2001)[22] suggested that Down syndrome patients with normal thyroid functions and those with compensated hypothyroidism should be followed annually and every 3 months, respectively. However other authors like Gibson PA et al (2005)[17] suggest initial testing results could be used as a basis to select a subgroup for further testing at say five yearly intervals unless new symptoms emerge in the interim and that that yearly screening (as recommended by the American Academy of Paediatrics, 2001) is probably not justified in the first 20 years of life.

Conclusion

To conclude, we propose that new born screening programmes, which test infants for hypothyroidism, could potentially adapt themselves to include routine testing for hypothyroidism in older infants and children with Down syndrome. This would allow for a relatively easy and inexpensive method for preventive health care in children with a handicapping condition.

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