

RESEARCH ARTICLE

Thyroid dysfunction in Congolese subjects with Down syndrome

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Abstract: Objective: The present study aims to assess the proportion and the pattern of thyroid dysfunction in a population of Congolese subjects with Down Syndrome. Methods: A total of 34 subjects with Down syndrome were recruited from Lubumbashi (Democratic Republic of Congo). Thyroid morphology was assessed by sonography. Serum T3, T4, FT4, TSH, Thyroglobulin, Thyroid peroxidase antibody (TPOAb) and anti-thyroglobulin antibody (TgAb) were measured. Results: The mean age of the patients was 13 years (range: 3 and 47 years). Of 34 Down syndrome subjects, 6 cases (17.6%) were found to have subclinical hypothyroidism. No patient had hyperthyroidism. Among 29 subjects with a thyroid ultrasound imaging, 25 patients (86.2%) were found to have morphological abnormalities of the gland. Regarding thyroid autoantibodies, TPOAb was positive in 1 case (2.9%) and TgAb was positive in 1 case (2.9%). The results were compared between patients with hypothyroidism and with normal thyroid function. There was no statistical difference in terms of age, sex, nutritional status, antibody levels and thyroid volume between these two groups. Conclusions: In our series, the proportion of hypothyroidism is relatively important but it remains largely under the prevalence reported in international studies.

Keywords: subclinical hypothyroidism, autoimmunity, Down syndrome, Congo

1 Introduction

Thyroid dysfunction (hypothyroidism and hyperthyroidism) is known to be more common in subjects with Down Syndrome than in the general population with a prevalence of 3 to 54% and its frequency increases with age^[1]. Moreover, it has been reported that subclinical hypothyroidism with mild plasma thyroid stimulating hormone (TSH) elevation is prevalent in Down syndrome with 80-90% in early infancy and 30-50% in adolescents and adults^[2]. Mechanisms leading to thyroid dysfunction in Down syndrome are not well known. Down's syn-

drome has been linked with other autoimmune disorders suggesting an aetiological association. Thus far, it has been proposed that the increased oxidative stress mainly caused by an excessive activity of Superoxide Dismutase-1 (SOD1), an enzyme coded on the human chromosome 21 (21q22.1), may be a major factor^[3-5]. In addition to SOD1, there are about 16 genes or predicted genes on HSA21 with a role in mitochondrial energy generation and ROS metabolism which can contribute to the increasing of the oxidative stress and thyroid function perturbations in patients with Down syndrome^[1,3]. Decreased levels of selenium, impairment in the activity of phenylalanine hydroxylase, and overexpression of DYRK1A kinase has been suggested as factors which may also influence the thyroid function in Down syndrome patients^[1]. However more but not all of Down syndrome patients develop thyroid function disorders. This fact suggests the existence of unknown factors which could be epigenetic or environmental.

The incidence of primary neonatal hypothyroidism has been found to vary depending on environmental factors (iodine sufficiency) and racial/ethnic background in general population. The incidence is higher in Hispanics and South Asians (1/2000) and lower in American Africans (1:32000)^[6]. This variability may also affect the prevalence of thyroid disorders in Black African subjects with Down Syndrome. There seems to have been no previous

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work on thyroid function of subjects with Down syndrome from central Africa.

The aim of the present study was to assess the profile of thyroid dysfunction in Down syndrome patients living in the Haut-Katanga province, in the southeast of the Democratic Republic of Congo (DRC).

2 Patients and methods

2.1 Study design and population

Thirty-four subjects with Down syndrome have been recruited at the Department of Pediatrics of the University Clinics of Lubumbashi as well as at the specialized school for Persons with Intellectual disabilities Balou in Lubumbashi (DRC) from January 1st, 2016 to December 31st, 2018.

Diagnostic criteria for Down syndrome was exclusively clinical: presence of intellectual disability, simian crease, sandal gap, epicanthic folds, up slanting palpebral fissures, and protruding tongue. Each participant gave a morning blood sample. Serum sample for thyroid function hormones and autoimmunity measurements were obtained by centrifugation of the blood sample immediately after collection. No treatment history.

2.2 Case definition

Thyroid Function: thyroid function was assessed by measuring serum TSH, T4 and T3 in the biomedical laboratory of the University of Lubumbashi, with ELISA immunoassays. Serum samples were analyzed in Lubumbashi for TSH, Total T4 and T3 by an immunoenzymatic colorimetric method with the ETI-System fast reader ELX 800, and using commercial kits supplied by “Human diagnostics” for Thyroid hormones screening according to the manufacturers protocol (Human Diagnostics). Serum analyses were completed in Belgium (Erasmé Laboratory of Medical Chemistry) for free T4 (FT4), thyroglobulin (Tg), antithyroglobulin and antithyroperoxidase antibody (TgAb & TPOAb) concentrations. Pediatric Reference Intervals for serum T4, T3, TSH and FT4 by Zurakowski *et al.*^[7] which take into account the significant effects of both age and sex and are based on a very large number of children, have been used to determine normal and pathologic findings.

Euthyroidism was defined as a normal TSH in mIU/L (ranges: 1-5 years: Males: 0.7-6.0, Females: 0.7-6.0; 6-10 years: Males: 0.7-5.4, Females: 0.6-5.1; 11-15 years: Males: 0.6-4.9, Females: 0.5-4.4; 16-20 years: Males: 0.5-4.4, Females: 0.5-3.9) with normal FT4 in pmol/L (ranges: 1-5 years: 9.0-37.2; 6-10 years: 8.3-34.1; 11-15 years: 7.6-31.1 and 16-20 years: 7.0-28.7). Subclinical

hypothyroidism was defined as an elevated TSH with normal FT4, overt hypothyroidism as high TSH with low FT4, isolated hypothyroxinemia as low FT4 with normal TSH, and subclinical hyperthyroidism was defined as low TSH with normal FT4. TPOAb and TgAb tests were positive, according to the laboratory normal values when > 34 U/ml and > 115 U/ml respectively.

Thyroid Morphology: Thyroid morphology was assessed in Lubumbashi (DRC) by sonography. The subject was asked to take a supine position with a pillow under the shoulder and the neck hyperextended. The sonographic examination was performed with specific attention to the thyroid gland size, shape and echo structure. The volume of each lobe was calculated by the formula: $V \text{ (ml)} = 0.000479 \times \text{length} \times \text{width} \times \text{thickness (mm)}$.

The volume of the whole thyroid gland was calculated as the sum of the two lobes. The volume of the isthmus was not included. Since Lubumbashi (DRC) is an area with a high prevalence of malnutrition, normal volume of the thyroid gland in children has been determined according to body surface area (BSA) reference as recommended by the WHO^[8].

The BSA was calculated using the following formula of Dubois and Dubois: $BSA \text{ (m}^2\text{)} = W^{0.425} \times H^{0.725} \times 71.84 \times 10^{-4}$ ^[9].

A thyroid gland was considered as hypertrophic when its volume was above the 97th percentile of the volume found in an iodine replete population used as control^[10].

2.3 Statistical Analysis

All data collected were analyzed and gathered using IBM SPSS statistics version 20 (Chicago, USA). Analysis and interpretation were done using the calculation of the proportion, the means and the standard deviation.

2.4 Ethics statement

Informed consent and child assent were obtained verbally by investigators who were fluent in Swahili, the local spoken language. Parents who allowed their children to participate in the study were then asked to sign the consent forms that were kept for records at the study office. Patients in the study were anonymized and assigned a unique study identifier number. Ethical approval of research activities was obtained from the Ethical Medical Committee of the University of Lubumbashi (CNES N°001/CNES/SR/03/2015).

3 Results

Thirty four subjects with Down syndrome were eligible (25 male, 9 female) according to typical dysmorphic features. The mean age of the patients was 13 years

Table 1. Functional and Morphological findings in Congolese Down syndrome patients

Variable	Number	Percentage
Function (n=34)		
Normal Thyroid function tests	28	82.40
Abnormal Thyroid function tests	6	17.60
Subclinical Hypothyroidism	6	17.60
Autoimmunity (n=34)		
TPOAb and TGAb -	32	94.12
TPOAb +	1	2.94
TGAb +	1	2.94
Morphology (n=29)		
Normal Thyroid	4	13.70
Abnormal Thyroid	25	86.20
Hypoechoogenicity	7	28.00
Uni or Multinodularity	2	6.90
Thyroid Hypertrophy	23	79.30
Thyroid Hypoplasia	2	6.90

(range: 3 and 47 years); 7 (20.6%) patients were over 16 years of age. Of 34 subjects with Down syndrome of our series, 6 (17.6%) were found to have subclinical hypothyroidism. No patient had hyperthyroidism. Subclinical hypothyroidism was found to be the unique functional abnormality. A morphological abnormality has been found in 86.2%. Enlargement of the thyroid gland was the most common morphological finding. Antibodies were found to be positive in 2 of our subjects (1 male and 1 female) [Table 1](#).

Thyroid volumes of 29 patients were measured using ultrasound. Median total thyroid volume was 6 mL (range: 2 - 16 mL) in euthyroid and 5.5 ml (range: 3 - 12 mL) in hypothyroid subjects with Down Syndrome. Of those 29 subjects with a thyroid ultrasound imaging, 25 subjects (86.2%) were found to have morphological abnormalities of the gland. Hypoplasia and hypertrophy were detected in 2 (6.9%) and 23 (79.3%) of them respectively. Thyroid uni/ multinodularity was found in 2 patients (6.9%). No patient had thyroid aplasia [Table 1](#).

Of six patients with hypothyroidism, one had normal thyroid volume whereas five had hypertrophy of the gland. Thyroid volume and echogenicity were found to be normal in 1 patient (16.6%) with hypothyroidism. Enlargement of the thyroid gland was found to be the most common morphological abnormality found in patients with hypothyroidism. Additionally, no positive thyroid antibodies were found in patients with hypothyroidism in our cohort [Table 2](#).

4 Discussion

Primary thyroid disorders are more frequent among children and adults with Down syndrome than in the general population^[11,12]. This first Congolese study displayed a spectrum of thyroid dysfunction similar to international cohorts, with subclinical hypothyroidism be-

ing the most common functional abnormality encountered in this population. In our study, thirty-four subjects with Down syndrome were eligible (25 male, 9 female). Among those 34 subjects, 6 (17.6%) were found to have subclinical hypothyroidism. However, no patient had hyperthyroidism whereas a prevalence of 3% has been found in most worldwide studies on thyroid function in Down syndrome population^[13].

Despite the relative important proportion of subclinical hypothyroidism in our series, thyroid disorders rates in Congolese subjects with Down syndrome than those reported in Asian and American populations^[11, 14, 15].

The influence of specific ethnic background in modeling the spectrum of thyroid disorders is well known. Incidences of neonatal primary hypothyroidism vary with racial and ethnic origin, with a ratio of 1/16 between African American and Hispanics/South Asian populations sharing the same North-American environment. The reasons of this variability with the racial origin remain elusive. Genetic polymorphisms are responsible for many of normal differences in endocrine function and susceptibility to disorders observed among populations^[16]. Moreover there is growing evidence now suggesting that epigenetics can explain inter-individuals and/or populations endocrine variability^[16,17]. These epigenetic changes have probably been induced by environmental exposures or lifestyle choices of ancestors and passed to the next generations. These factors may also explain the differences we have observed in hypothyroidism prevalence among Down syndrome patients with different ethnic background.

Another hypothesis may be formulated according to the postulated theory that the increased oxidative stress, mainly caused by an excessive activity of SOD1, may be a major factor explaining the frequent occurrence of thyroid disorders in subjects with Down Syndrome. In addition to SOD1, there are about 16 genes or predicted genes on the human chromosome 21 with a role in mitochondrial energy generation and ROS metabolism which can contribute to the increasing of the oxidative stress^[3,4]. In conditions of increased oxidative stress, Glutathione plays a fundamental role in the detoxification of free radicals. Ethnic variation in red cell glutathione peroxidase activity has been reported in several studies^[18]. This variability may lead to a variable adaptation of the thyroid gland to oxidative stress and thus, to different thyroid dysfunction prevalence among patients of different ethnic background.

There is a great phenotypic variability between Down syndrome subjects with classical trisomy 21 and those with mosaicism. One weakness of this study is the absence of molecular diagnosis of Down syndrome.

Table 2. TSH, FT4 and morphological findings in subjects with subclinical hypothyroidism

Variable	Patient					
	1	2	3	4	5	6
Age (years)	4	8	9	11	21	23
Sex	M	M	F	M	M	M
Thyroid Function						
TSH (mUI/L)	7.26	6.99	6.62	5.18	5.44	10.31
FT4 (ng/dl)	1.5	1	1.8	1.2	1.6	1.2
T3 (ng/ml)	2.01	2.15	1.93	1.05	1.1	1.93
Thyroglobulin (g/l)	44	22.5	133	19.6	45	34.6
Thyroid Morphology						
Hypertrophy*	Yes	No	Yes	Yes	Yes	Yes
Hypotrophy*	No	No	No	No	No	No
Hypoechoogenicity	No	No	No	No	No	No
Nodules	No	No	No	No	No	No
Thyroid autoimmunity						
TPOAb (U/ml)	6	7	12	9	9	14
TgAB (U/ml)	11	11	13	11	11	16
Positive Thyroid antibodies**	No	No	No	No	No	No

Note: * According to BSA in relation to thyroid volume references as recommended by WHO; ** Normal values: TgAb < 115 U/ml and TPOAb < 34 U/ml

Thyroid volumes of 29 subjects were measured using ultrasound. Interpreting morphological findings from pediatric populations is complicated when we take into account the controversy surrounding the norms for thyroid ultrasonography mensuration in pediatric population. Age-related, length-related, weight-related as well as BSA-related norms have been proposed in several publications^[8, 19, 20]. No universal reference values for thyroid volume measured by ultrasonography in schoolchildren of iodine sufficient populations are presently available. Thus, interpreting thyroid volume from our Central African children using reference ranges derived from Asian or European subjects may result in underestimation of thyroid gland hypertrophies and/or overestimation of thyroid gland hypotrophies. Therefore, validity of morphological findings interpretation should depend on comparison with norms from population of the same racial and ethnic origin. In absence of African norms, our interpretation was function of sex, and BSA. This approach, which takes into account the differences in body development among children of the same age, is strongly recommended by the WHO specifically in countries such as the DRC with high prevalence of child growth retardation due to malnutrition with both stunting and underweight. Of 29 investigated subjects, 25 (86.2%) were found to have morphological abnormalities of the gland (6.9% hypoplasia and 79.3% hypertrophy). However, no statistical difference was found between euthyroid and subclinical hypothyroid patients regarding thyroid volume. The high rate of thyroid hyperplasia might be justified with iodine deficiency. The Democratic Republic of Congo had historically been a severely iodine deficient area. Combined iodine and selenium deficiency has been found in Equateur, Haut-Zaire and Kivu, where endemic myxoedematous cretinism occurs, but also in Katanga (former Shaba)^[21]. In October

1993, the DRC adopted a strategy to control Iodine deficiency disorders. This strategy has been implemented since 1994, particularly the prohibition of the import of noniodized salt and the control of salt iodine levels at retail points in the country. As a result of this public health strategy, the DRC is moving close to successful elimination of Iodine deficiency disorders. Since this specific public health problem is about to be resolved we decided not to test our patients for urinary iodine concentrations.

Our study reinforces the importance of establishing our own standards which can be used in daily practice. Further case-control studies including non-Down syndrome subjects should be carried out in order to compare our findings with those from general population from the same area.

Approximately 4.8% of patients had positive antibodies. TPOAb were found to be positive in one young child (2.4%) and TgAb in one adult (2.4%). An association was found in several studies between the presence of thyroid antibodies and resulting hypothyroidism.¹¹ According to these findings, thyroid antibodies have been told to constitute a marker for thyroid dysfunction in people with Down syndrome^[11]. However, no positive thyroid antibodies were found in patients with hypothyroidism in our series. Moreover, no statistical difference was found between subjects with and without hypothyroidism regarding mean antibodies levels. Additionally, lower Positive TPOAb/TGAb rates were found in our Congolese series than American^[15, 22–24], Britain^[25] and Kuwaiti^[11] populations with Down syndrome ($p < 0.01$). However the rate of positive thyroid antibodies was not different from those found in an Italian study ($p = 0.09$)^[26]. Thus, it would seem that thyroid autoimmunity is not the main risk factor leading to hypothyroidism in Congolese subjects with Down Syndrome. Low Positive TPO antibodies rates

have also been found in pregnant woman from Lubumbashi^[27]. However, further studies including a greater sample size as well as a control group from the same ethnic background are necessary to confirm this trend.

Regarding the relatively low prevalence of hypothyroidism, the absence of hyperthyroidism and the low rate of positive thyroid antibodies tests in our series, and given the resource constraints placed on the healthcare system by the burden of malnutrition, endemic tropical infectious diseases (Malaria) and recurrent Cholera, Ebola and Measles outbreaks, the question of implementation of a systematic annual screening for thyroid disorders in patients with Down syndrome should be raised in the DRC. For such an implementation, hormone measurements are required. However, such testing is almost unavailable in primary, secondary, and even in some tertiary care hospitals^[28].

5 Conclusion

In our series, the proportion of subclinical hypothyroidism is relatively important but it remains largely under the prevalence reported in international studies. Epidemiological data available from DRC are inadequate to provide firm details on the number of patients with Down syndrome. A cost-effective strategy, taking into account both public health priorities as well as a genuine interest for patients living with rare diseases, should be found for low-income countries.

Data Availability

The datasheet used to support the findings of this study are available from the corresponding author upon request.

Competing interests

The authors declare that they have no competing interests.

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